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Valence Isomerizations in Compounds with Strained Rings

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Dedicated to Prof. Dr. Otto Bayer on the occasion of his 60th birthday

Among the many molecular rearrangements that may occur in compounds with strained rings, valence (or valence bond) isomerizations have recently received special attention. Relief of strain in energy-rich small or medium-sized rings is the driving force behind these predominantly thermal (pyrolysis) reactions. In many instances, valence isomerizations must be considered as multicenter rearrangements (with six- or four-membered cyclic transition states). This mechanism can be regarded as firmly established for Cope rearrangements, as well as for intracyclic diene syntheses and diene cleavages of strained rings, with which this paper deals.

Introduction

In the last decade numerous isomerization reactions have become known which differ phenomenologically as well as mechanistically from most of the common molecular rearrangements. It is characteristic for these isomerizations that they proceed without migration of atoms or groups of atoms. As illustrated by the reversible transformation of cycloocta-1,3,5-triene into bicyclo[4,2,0]octa-2,4-diene [1] the structural change consists solely of a "reorganization" of the σ- and π-electrons within the framework of the molecule, accompanied by corresponding changes in atomic distances and bond angles.

Grob and *Schiess* [2] introduced the general term "valence isomerization" for this type of rearrangement. If a dynamic equilibrium is established between the two isomers – as in the system mentioned above – it is also referred to as valence tautomerism [3].

The majority of valence isomerizations must be regarded as multicenter processes, constituting a type of reaction which has only recently received adequate attention. Multicenter processes involve no common intermediates such as ions or free radicals and thus show little response to catalysts and changes in the medium. They generally pass through cyclic transition states, in which simultaneously (or almost simultaneously) new bonds are formed while old ones are broken. In addition to valence isomerizations, this reaction type includes such important synthetic methods as the Diels-Alder reaction, the 1,3-dipolar addition, and other cyclo-additions.

For several valence isomerizations, however, a radical mechanism cannot be excluded.

Cope Rearrangements

One of the best examples of a valence isomerization of the multicenter reaction type is the thermal rearrangement of diallyl compounds to isomeric diallyl compounds discovered by *A. C. Cope* and his associates [4].

[*] Excerpts from lectures presented at the 141st National Meeting of the American Chemical Society (Symposium on Small Ring Compounds) in Washington D.C., March 26th, 1962, and at several American universities and research institutes.

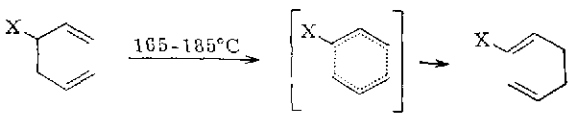
[1] *A. C. Cope, A. C. Haven* jr., *F. L. Ramp*, and *E. R. Trumbull*, J. Amer. chem. Soc. *74*, 4867 (1952).

[2] *P. W. Schiess*, Ph.D. Thesis, Universität Basel (1958), *C. A. Grob* and *P. Schiess*, Angew. Chem. *70*, 502 (1958). I am indebted to Prof. *Grob* for allowing me to peruse the thesis of *P. W. Schiess*.

[3] *J. W. Baker:* Tautomerism. George Routledge and Sons, London 1934, p. 201.

[4] A survey of Cope rearrangements is given by *J. Hine* in: Physical Organic Chemistry. McGraw-Hill, New York, 1962, p. 505.

This rearrangement proceeds especially easily, *i.e.* at temperatures as low as 165 -185 °C, if the diallyl system

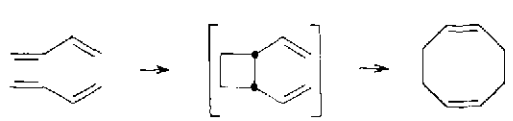


X = C_6H_5; CN; $COOCH_3$

has unsaturated substituents in the 3-position. The tendency of the substituent to enter into conjugation with the double bond apparently acts as the driving force. Based on kinetic studies, a cyclic mechanism has been postulated for this valence isomerization, just as for the related Claisen rearrangement. Such reactions are of the first order. Their intramolecular course is demonstrated by the fact that, during the rearrangement of a mixture of two diallyl compounds of comparable rates of reaction, no exchange of allyl groups is observed. An argument against a possible cleavage of the diallyl system in the rate-determining step [5] is provided above all by the considerably negative values of the entropies of activation (approximately -12 cal./degree·mole) measured for several Cope rearrangements. These data can be accommodated best by the assumption of a cyclic transition state.

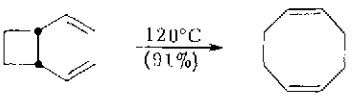
a) cis-1,2-Divinylcycloalkanes

We encountered the Cope rearrangement during an investigation [6] of the mechanism of the thermal, non-catalytic dimerization of butadiene to *cis,cis*-cycloocta-1,5-diene. This reaction was discovered by *Ziegler* and *Wilms* [7] and proceeds at temperatures of 120 -300 °C in the presence of inhibitors of chain polymerization. This dimerization was first interpreted as a 1,4:1,4-addition of two butadiene molecules. Since in conventional ring-closure reactions the eight-membered ring forms in satisfactory yield only when the Ruggli-Ziegler dilution principle is applied, we did not consider the 1,4:1,4-addition to be likely. In our opinion, the eight -membered ring formation from butadiene represents a two-step reaction. Initially, a 1,2:1,2-addition of two butadiene molecules takes place to give a four-membered ring compound, *cis*-1,2-divinylcyclobutane.

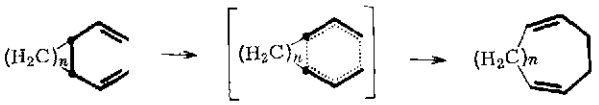


This intermediate has so far not been isolated as a dimerization product. We assume that it is thermally unstable and that it isomerizes under the conditions of formation in a Cope rearrangement to give *cis,cis*-cycloocta-1,5-diene. As the driving force for this transformation one has to consider the release of strain associated with the cleavage of the four-membered ring.

To substantiate our hypothesis for the mechanism of the butadiene dimerization, we synthetized the postulated intermediate, *cis*-1,2-divinylcyclobutane, in an independent way. As was expected, this hydrocarbon rearranged even at 120 °C into *cis,cis*-cycloocta-1,5-diene, which was isolated as the only distillable product in a yield of 91 %.

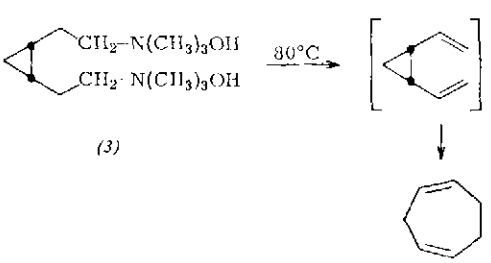


In order to determine the influence of ring strain (Baeyer strain) on the rate of the Cope rearrangement of *cis*-1,2-divinylcycloalkanes *(1)*, the homologues of *cis*-1,2-divinylcyclobutane had to be synthetized and their thermal behavior investigated [8]. A definite relationship between ring strain and the tendency to undergo valence isomerization to the corresponding cycloolefins *(2)* was to be expected, especially for *cis*-1,2-divinylcycloalkanes *(1)* with n = 1 -3, since approximately the same steric conditions for the formation of the cyclic transition state of the Cope rearrangement are present in each of these hydrocarbons.



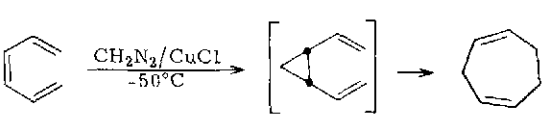
(1) *(2)*

We first investigated *cis*-1,2-divinylcyclopropane, which, in all probability, should be unstable. In an effort to obtain the hydrocarbon by Hofmann degradation of the base *(3)* at 80 °C, we isolated only its isomerization products, cyclohepta-1,4-diene and cyclohepta-1,3-diene, the latter being formed by prototropy.



(3)

Doering and *Roth* [9] have meanwhile found that addition of methylene (prepared from diazomethane and CuCl) onto *cis*-hexatriene at −50 °C also yields only cyclohepta-1,4-diene and its conversion products.



In contrast to *cis*-1,2-divinylcycloalkanes with small strained rings, the homologous *cis*-1,2-divinylcyclopentane is stable up to 250 °C. Even at higher temperatures, it cannot be converted into the nine-membered

[5] For radical-type cleavage of diallyl compounds, see *H. P. Koch*, J. chem. Soc. (London) *1948*, 1111; *W. D. Huntsman*, J. Amer. chem. Soc. *82*, 6389 (1960).

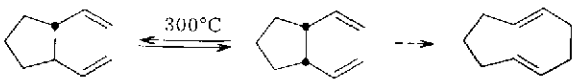
[6] *E. Vogel*, Liebigs Ann. Chem. *615*, 1 (1958).

[7] *K. Ziegler* and *H. Wilms*, Liebigs Ann. Chem. 567, 1 (1950).

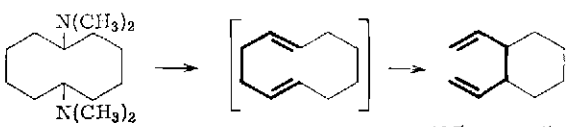
[8] *E. Vogel, K.-H. Ott* and *K. Gajek*, Liebigs Ann. Chem. *644*, 172 (1961).

[9] *W. v. E. Doering*, personal communication.

ring compound, cyclonona-1,5-diene. Instead, the establishment of a cis-trans equilibrium is observed [8].

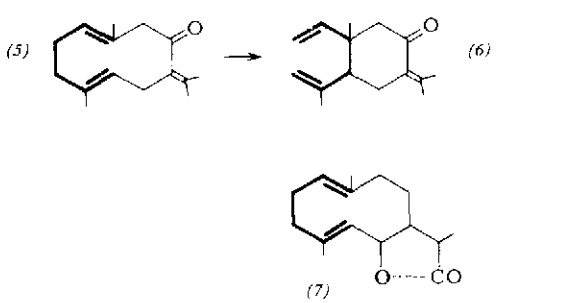


The failure of cis-1,2-divinylcyclopentane to undergo the Cope rearrangement, even under extreme conditions, must obviously be attributed to the fact that in the system cis-1,2-divinylcyclopentane/cyclonona-1,5-diene the reverse ring strain relationship obtains as in the systems discussed earlier. In this case it is not the starting material but the product of rearrangement that shows significant strain (nonclassical strain) [10].Therefore, we believe cyclonona-1,5-diene to be unstable and to isomerize easily to 1,2-divinylcyclopentane, thus reversing the desired rearrangement. More recent investigations on cyclodeca-1,5-dienes strongly support this assumption. According to *Grob* and *Schiess* [2], cyclodeca-1,5-diene, formed by *N*-oxide elimination and Hofmann degradation of the *cis*- and *trans*-forms of the diamine *(4)*, undergoes rearrangement under the reaction conditions to 1,2-divinylcyclohexane (40% *trans* and 1% *cis*) and other isomeric hydrocarbons.



(4)

The same rearrangement has recently been observed in naturally occurring ten-membered carbocyclic compounds, *viz.* the sesquiterpenoids germacrone *(5)* [11] and dihydrocostunolide *(7)* [12]. On distillation *in vacuo* (b.p. = 165 °C/ 10 mm), germacrone is converted into β-elemenone (pyrogermacrone) for which the structure *(6)* has been elucidated.



(7)

A cyclohexane derivative corresponding to *(6)* has been obtained by pyrolysis of dihydrocostunolide *(7)*. The occurrence of these isomerizations also furnishes proof for the position of the endocyclic double bonds in germacrone and dihydrocostunolide.

[10] For discussions of non-classical strain in medium-sized rings, see *R. Huisgen*, Angew. Chem. *69*, 341 (1957); *V. Prelog* in *A. R. Todd:* Perspectives in Organic Chemistry. Interscience, New York 1956, p. 96; *J. D. Dunitz* and *V. Prelog*, Angew. Chem. *72*, 896 (1960).

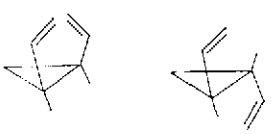
[11] For summaries of information on germacrone and other terpenes with medium-sized rings, see *F. Sorm* in *L. Zechmeister:* Advances in the Chemistry of Organic Natural Products. Springer, Vienna 1961, vol. 19, p. 1; *T. G. Halsall* and *D. W. Theobald*, Quart. Reviews *16*, 101 (1962).

[12] *A. S. Rao, A. Paul, Sadgopal* and *S. C. Bhattacharyya*, Tetrahedron *13*, 319 (1961).

Taking into account these rearrangements of cyclodeca-1,5-dienes, our studies on the valence isomerization of *cis*-1,2-divinylcycloalkanes lead to the conclusion that the thermal behavior of these hydrocarbons is determined by the strain present in either the starting material or the final product. While in *cis*-1,2-divinylcycloalkanes with small rings, rearrangement to valence-isomeric cyclo-olefins occurs very easily as a consequence of Baeyer strain, the reverse reaction is favored with *cis*-1,2-divinylcyclohexane (and most likely with *cis*-1,2-divinylcyclopentane), because of the strong nonclassial strain present in the products of rearrangement.

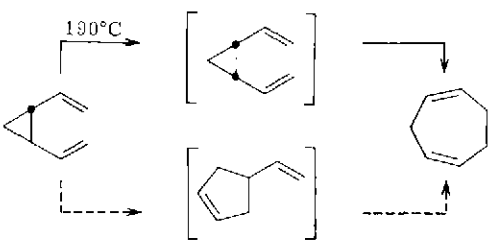
b) trans-1,2-Divinylcycloalkanes

In trans-1,2-divinylcycloalkanes with small rings the cyclic transition state postulated for the Cope rearrangement cannot be attained for geometrical reasons. Hence, the thermal behavior of *trans*-1,2-divinylcyclopropane and -cyclobutane should reveal stereochemical information about the mechanism of this reaction.



(8) *(9)*

While *cis*-1,2-divinylcyclopropane is transformed spontaneously into cyclohepta-1,4-diene, the *trans*-compound *(9)* undergoes isomerization only on heating to 190 °C for 2 hours, cyclohepta-1,4-diene also being obtained. The yield is essentially quantitative [13].



(10)

We assume the rate-determining step of the rearrangement to be a *trans-cis* isomerization [14], which presumably proceeds via a diradical. 4-Vinylcyclopentene *(10)* can be excluded as an intermediate, since this hydrocarbon does not isomerize, even at 300 °C [15].

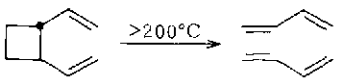
The *cis*- and *trans*-1,2-divinylcyclobutanes differ not only in their stability but also in their pyrolysis products [13]. As previously reported, the *cis*-isomer rearranges completely to an eight-membered ring at 120 °C; *trans*-1,2-divinylcyclobutane *(11)*, on the other hand, is stable up to about 200 °C and at higher temperatures

[13] *E. Vogel*, in: Festschrift zum 10-jährigen Bestehen des Fonds der Chemischen Industrie. Verband der Chemischen Industrie, Düsseldorf 1960, p. 225.

[14] *B. S. Rabinovitch, E. W. Schlag* and *K. B. Wiberg*, J. chem. Physics *28*, 504 (1958).

[15] *B. Peltzer*, Diploma Thesis, Universität Köln 1962.

decomposes mainly into butadiene, which partly dimerizes under these conditions to 4-vinylcyclohexene



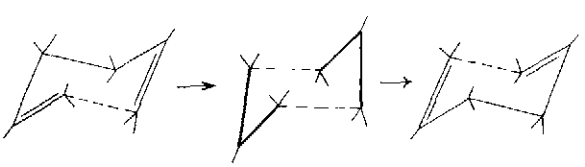
(11)

and *cis,cis*-cycloocta-1,5-diene. To a minor extent *trans-cis* isomerization must also occur in the pyrolysis of *trans*-1,2-divinylcyclobutane, as shown by the fact that the pyrolyzate contains more *cis,cis*-cycloocta-1,5-diene than the mixture of dimers obtained from butadiene at the same temperature. Competition between *cis-trans* isomerization and cleavage in the pyrolysis of cyclobutane derivatives has already been observed [16].

The results of this investigation give stereochemical support for the cyclic transition state of the Cope rearrangement which was, previously deduced from kinetic data.

A better understanding of the geometry of this transition state is provided in a paper by *Doering* and *Roth* [17]. Two different spatial arrangements are possible for the transition state of the rearrangement of flexible diallyl compounds: a quasi-boat form with two parallel allyl groups (six-center overlapping) and a quasi-chair form in which only the ends of the two allyl triads are in interaction (four-center overlapping).

six-center overlapping (boat form)

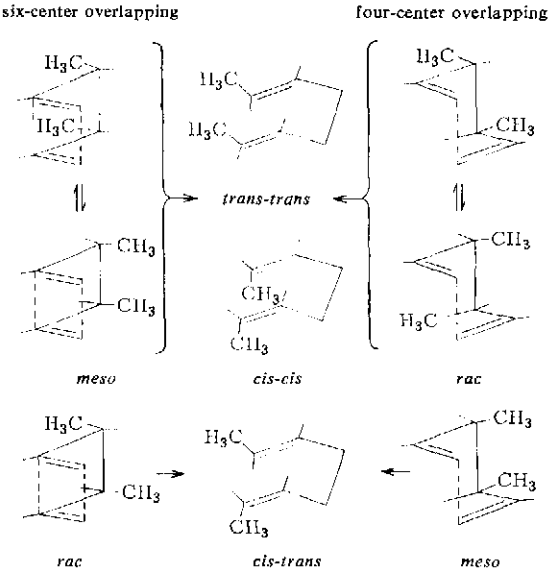


four center overlapping (chair form)

The question which of the two arrangements is energetically more favored was settled in the case of the stereoisomeric 3,4-dimethylhexa-1,5-dienes. For a transition state with six overlapping centers, the *meso*-form would result in a mixture of *trans,trans*- and *cis,cis*-octa-2,6-dienes and the racemic form in *cis,trans*-octa-2,6-diene alone. If, however, four-center overlapping is preferred, then the outcome would be reversed, a mixture of *trans,trans*- and *cis,cis*-octa-2,6-diene being obtained from the racemic form and *cis,trans*-octa-2,6-diene from the *meso*-form.

The *meso*-form partially rearranges at 225 °C (6 hours) to a mixture of 99.7 % *cis,trans*- and 0.3 % *trans,trans*-octa-2,6-diene, while the racemic form at 180 °C (18 hours) is converted almost quantitatively into *trans,trans*- and *cis,cis*-octa-2,6-diene, the ratio of the two products being 9 to 1.

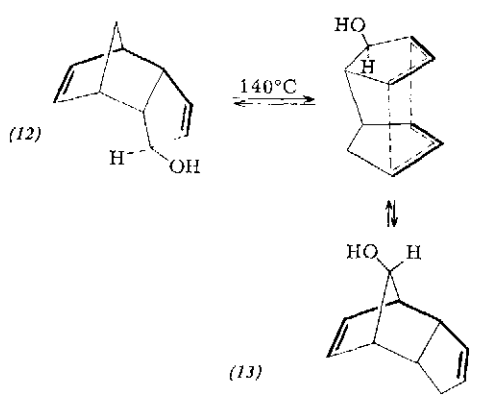
From the foregoing, it follows that in these examples, where a free choice of the geometry of the transition state is possible, the four-center transition state is favored over the six-center state by a factor of more than 300 or by at least 5.7 kcal/mole. This preference for the four-center transition state is reminiscent of the energy relationships in the chair and boat forms of cyclohexane. The chair-like arrangement may thus



be inferred to have less conformational strain. In addition, theoretical considerations lead to the conclusion that there are no attracting forces between the two middle carbon atoms of the two allyl groups. Therefore, the four-center arrangement should be the more stable one [17].

c) endo-Dicyclopentadienes

Woodward and *Katz* [18] have recently recognized that Cope rearrangements may also occur in *endo*-dicyclopentadienes. According to their observations, α-1-hydroxydicyclopentadiene *(12)* is partially converted into the isomeric *syn*-8-hydroxydicyclopentadiene *(13)* at 140 °C, a temperature considerably lower than the dissociation temperature of dicyclopentadiene (about 200 °C). This involves an equilibrium reaction, since, on heating, each of the two alcohols gives the same mixture of *(12)* and *(13)*. The equilibrium constant



(12)

(13)

of the reaction is approximately 1. Correspondingly, at 140 °C, β-1-hydroxydicyclopentadiene *(14)* gives *anti*-8-hydroxydicyclopentadiene *(15)*. Here, however, for steric reasons the equilibrium lies almost entirely on the side of the alcohol *(15)*. The mild reaction conditions and in particular the stereospecifity of these isomerizations rule out a dissociation-recombination mechanism and are suggestive of a Cope rearrangement. The final proof for this course of the reaction was

[16] *H. R. Gerberich* and *W. D. Walters*, J. Amer. chem. Soc. *83*, 3935, 4884 (1961).

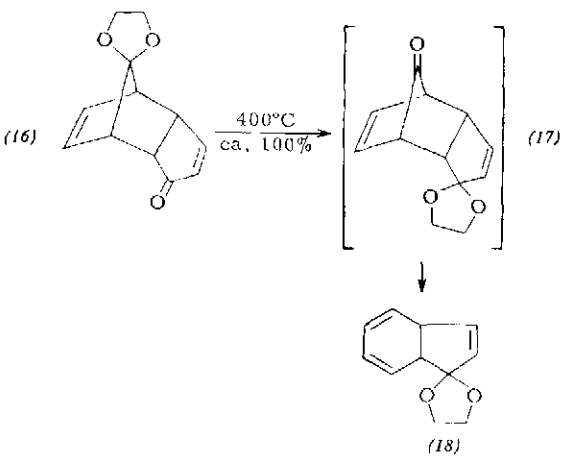
[17] *W. v. E. Doering* and *W. R. Roth*, Tetrahedron *18*, 67 (1962).

[18] *R. B. Woodward* and *T. J. Katz*, Tetrahedron *5*, 70 (1959).

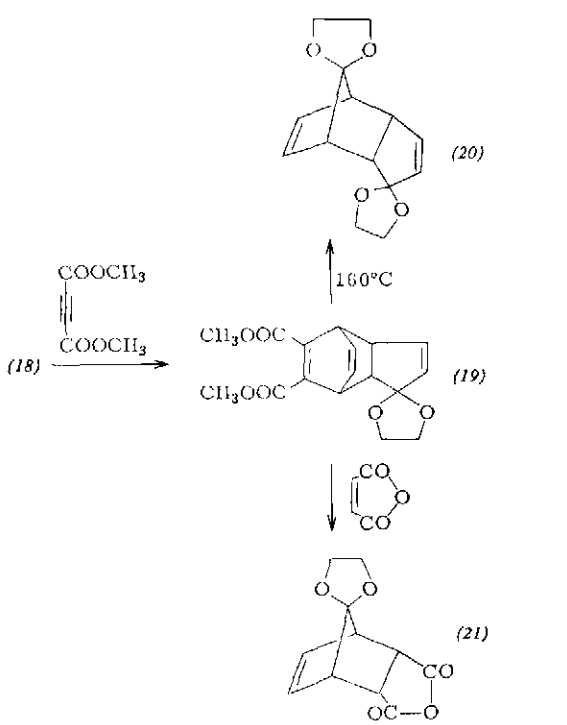
furnished by the finding that optical integrity is preserved in the isomerization of optically active α- and β-alcohols *(12)* and *(14)*.

The ketone obtained by oxidation of 8-hydroxydicyclopentadiene [18,19] and its tetrachloro derivative [20] also undergo the Cope rearrangement. They are converted completely into the more stable isomers with the carbonyl group in the 1-position. It is noteworthy that the isomerization of these two ketones is catalyzed by protic and Lewis acids.

From our own observations, we conclude that a Cope rearrangement is also involved in the gas-phase pyrolysis of the ethylene ketal *(16)* of dimeric cyclopentadienone [21]. This was studied in connection with attempts to



synthetize the ethylene ketal of cyclopentadienone [22,23]. At 400 °C, *(16)* is converted almost quantitatively into the ethylene ketal of 8,9-dihydroindenone



[19] *R. C. Cookson, J. Hudec* and *R. O. Williams*, Tetrahedron Letters *1960*, No. 22, p. 29.

[20] *P. Yates* and *P. Eaton*, Tetrahedron *12*, 13 (1961).

[21] *C. H. DePuy* and *C. E. Lyons*, J. Amer. chem. Soc. *82*, 631 (1960); *K. Hafner* and *K. Goliasch*, Chem. Ber. *94*, 2909 (1961).

[22] *E. Vogel* and *E.-G. Wyes*, Angew. Chem. internat. Edit. *1*, 404 (1962).

[23] *C. H. DePuy* and *B. W. Ponder*, Angew. Chem. internat. Edit. *1*, 404 (1962).

(18). The latter must result from elimination of carbon monoxide from the intermediate *(17)*, which has so far not been isolated. It appears that a retro-diene decomposition of *(16)* can be excluded, since the other two feasible recombination products, namely the ethylene ketal of dimeric cyclopentadienone and α-indanone [21], could not be detected – not even in traces.

The pyrolysis product *(18)* opened a new route to the ethylene ketal of cyclopentadienone by its conversion with dimethyl acetylenedicarboxylate into the adduct *(19)* and by thermal decomposition of the latter according to the procedure of *Alder* and *Rickert*. So far, the ethylene ketal of cyclopentadienone, which dimerizes very easily, has not been isolated. It has, however, been trapped with dienophiles to form derivatives of 7-ketonorbornene *(21)* [22].

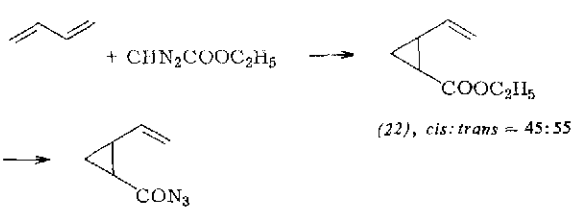
Novel Variations of the Cope and Claisen Rearrangements

It appeared to us that the Cope rearrangement of *cis*-1,2-divinylcycloalkanes with small strained rings is merely a special case of a more general rearrangement principle. In particular, cyclopropane compounds derived from *cis*-1,2-divinylcyclopropane by exchange of a vinyl group for another double bond function, *e.g.* isocyanate, ketene, azomethine, or carbonyl groups, should be able to undergo valence isomerizations analogous to the Cope reaction.

a) Valence Isomerizations of 2-Alkenylcyclopropyl Isocyanates

Such isomerizations have indeed been effected with 2-alkenylcyclopropyl isocyanates [24,25].

We chose to investigate the isomeric *cis*- and *trans*-2-vinylcyclopropyl isocyanates *(24)* and *(27)*. The synthesis of these compounds started out from ethyl 2-vinylcyclopropanecarboxylate *(22)* which was obtained in 80% yield by the reaction of ethyl diazoacetate with butadiene. The ester *(22)* consisted of the *cis*- and *trans*-forms in the ratio of 45:55.



(22), *cis*:*trans* = 45:55

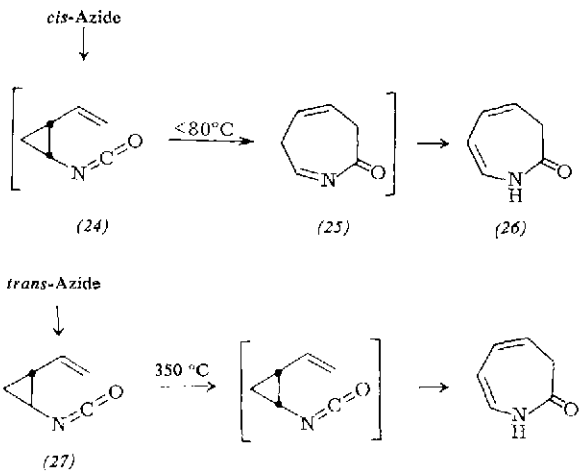
(23), *cis* and *trans*

The ester mixture was converted into *cis*- and *trans*-2-vinylcyclopropanecarbonyl azides *(23)*. These were subsequently submitted to the Curtius degradation at 80 °C to give the lactam *(26)* and *trans*-2-vinylcyclopropyl isocyanate *(27)*. The lactam evidently arises from an isomerization of unstable *cis*-2-vinylcyclopropyl

[24] *F. Vogel* and *R. Erb*, Angew. Chem. internat. Edit. *1*, 53 (1962).

[25] *W. v. E. Doering* and *M. J. Goldstein*, Tetrahedron *5*, 53 (1959).

isocyanate *(24)* derived from the *cis*-azide. An obvious intermediate in this rearrangement would seem to be the iminoketone *(25)* which in turn undergoes a prototropic shift. The migration of the double bond must be

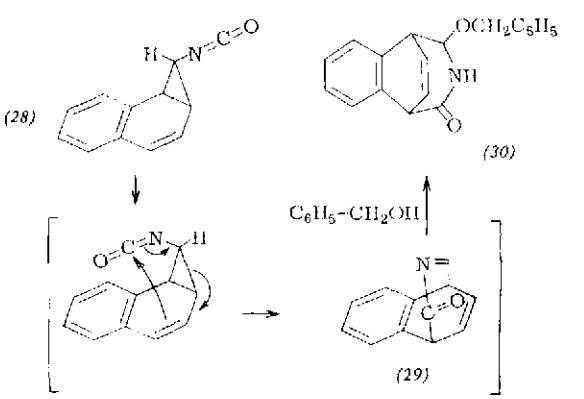


(24) *(25)* *(26)* *(27)*

due to the gain in resonance energy associated with the formation of the amide group. The *trans*-2-vinylcyclopropyl isocyanate is remarkably stable as compared with the *cis*-isomer: heating to 200 °C does not change the compound except for some slight polymerization. On gas phase pyrolysis at 350 °C, however, the *trans*-isocyanate is also converted into the lactam *(26)* probably through a prior *trans-cis* isomerization.

Thus, the two systems *cis*- and *trans*-1,2-divinylcyclopropane and *cis*- and *trans*-2-vinylcyclopropyl isocyanate qualitatively exhibit the same thermal behavior.

An additional example of valence isomerization of a 2-alkenylcyclopropyl isocyanate is the "unusual rearrangement of an acyl azide" described by *Doering* and *Goldstein* [25]. According to these authors, Curtius degradation of benzonorcaradienecarbonyl azide in the presence of benzyl alcohol does not yield the urethane derived from the isocyanate *(28)* but rather the isomeric lactam *(30)*. The course of this



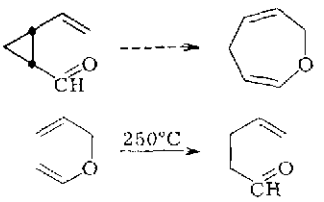
reaction differs from the rearrangement of 2-vinylcyclopropanecarbonyl azide only insofar as the iminoketone intermediate *(29)* is stabilized by the addition of benzyl alcohol. In this case a prototropic shift is not possible for steric reasons. More recent results have shown that the *exo*-configuration *(28)* holds for benzonorcaradiene carboxylic acid [26] and therefore in all probability also for benzonorcaradienyl isocyanate. This configuration of the isocyanate would explain why it isomerizes to *(29)* only on heating.

[26] *R. Huisgen* and *G. Juppe*, Chem. Ber. *94*, 2332 (1961).

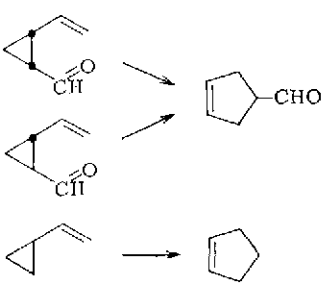
b) Valence Isomerization of 2-Vinylcyclopropanecarboxaldehyde

The isomerizations observed with the *cis*- and *trans*-2-vinylcyclopropyl isocyanates led us to study also the thermal behavior of *cis*- and *trans*-2-vinylcyclopropanecarboxaldehydes.

We were particularly interested in the properties of *cis*-2-vinylcyclopropanecarboxaldehyde, since its possible isomerization to a cyclic ether (2,5-dihydrooxepine) would represent a reverse Claisen rearrangement. It is known that vinyl allyl ethers rearrange to unsaturated aldehydes or ketones at temperatures as low as 250 °C. Such rearrangements, however, cannot be reversed, as far as we are aware [27].



The *cis*- and *trans*-2-vinylcyclopropanecarboxaldehydes were synthetized by known methods [28], starting from the adduct of butadiene and ethyl diazoacetate mentioned already. In contrast to the systems investigated earlier, in this case not only the *trans*- but also the *cis*-isomer could be isolated. The two aldehydes show surprisingly high thermal stability. In order to achieve isomerization, it was necessary to pyrolyze them in the gas phase at 400 °C. Under these conditions, both gave a good yield of the same product, identified as Δ^3-cyclopentenecarboxaldehyde.



The course of this thermal reaction shows that even ring strain does not provide sufficient driving force to bring about a retro-Claisen rearrangement. Instead of a rearrangement to the seven-membered ring, a valence isomerization takes place in which only the vinylcyclopropane system of the molecule participates. Thermal isomerization of vinylcyclopropane to give cyclopentene has recently been observed by *Overberger* and *Borchert* [29] and by *Vogel* et al. [30]. According to kinetic data by *Flowers* and *Frey* [31], this rearrangement also seems to be a multicenter reaction.

[27] *C. D. Hurd* and *M. A. Pollack*, J. Amer. chem. Soc. *60*, 1905 (1938); *F. W. Schuler* and *G. W. Murphy*, ibid. *72*, 3155 (1950); *L. Stein* and *G. W. Murphy*, ibid. *74*, 1041 (1952); *Y. Packer*, Proc. chem. Soc. (London) *1961*, 141.

[28] Unpublished studies, made together with *R. Erb*.

[29] *C. G. Overberger* and *A. E. Borchert*, J. Amer. chem. Soc. *82*, 1007 (1960).

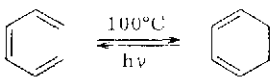
[30] *E. Vogel*, *R. Palm*, and *K.-H. Ott*, Angew. Chem. *72*, 21 (1960).

[31] *M. C. Flowers* and *H. M. Frey*, J. chem. Soc. (London) *1961*, 3547.

Intracyclic Diene Syntheses and Diene Cleavages

A valence isomerization similar to the Cope rearrangement is the cyclization of conjugated *cis*-trienes to cyclohexa-1,3-dienes, a reaction that often can be reversed. This isomerization, considered by *Alder* [32] to be an intracyclic diene synthesis, also shows the characteristics of a multicenter-type reaction; the same is true for the retro-reaction, the cleavage of the cyclic diene to the triene.

cis-Hexatriene [33], which has only recently been obtained in pure form, isomerizes completely to cyclohexa-1,3-diene, the reaction taking place at temperatures as



low as 100 °C [34]. It is possible to reverse this cyclization by irradiation of the diene with ultraviolet light [35].

a) The Valence Isomeric System Cycloheptatriene ⇌ Norcaradiene

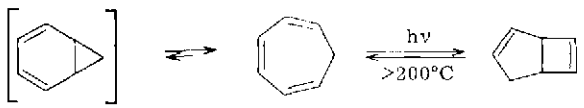
The most interesting valence isomerizations of this type are observed with cylic *cis*-trienes of structure *(31)*. Here a cyclic shift of electrons leads to bicyclic dienes *(32)*.

(31) *(32)*

When n = 1, then formulae *(31)* and *(32)* represent the system cycloheptatriene ⇌ norcaradiene which has recently been extensively investigated.

The system was discovered over 60 years ago by *Willstätter* [36] during his work on the elucidation of the structure of tropilidene, which had been isolated from atropine by *Ladenburg* [37]. *Willstätter* considered the three valence isomeric hydrocarbons cycloheptatriene, norcaradiene, and bicyclo-[3,2,0]-hepta-2,6-diene as possible structures for tropilidene. Since he succeeded in converting cycloheptene into tropilidene by different routes, he believed the cycloheptatriene formula to be correct.

The question of the structure of tropilidene cropped up again when *Meerwein* [38] obtained it by the addition of methylene to benzene, in which one would have expected norcaradiene as the product. Investigations stimulated by this observation showed that tropilidene can react in the form of both cycloheptatriene and norcaradiene. Thus, the chemical behavior of the compound does not permit reliable conclusions as to the nature of its ring system [39].



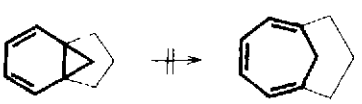
Employing nuclear magnetic resonance *Corey*, *Burke*, and *Remers* [40] confirmed the cycloheptatriene structure. The pseudoaromatic character [41] of tropilidene (resonance stabilization by 1,6-overlapping of the π-electron system), which has been proposed in the last few years, seems questionable in the light of results of equilibrium studies on seven-membered cyclic trienes [42].

The question whether cycloheptatriene is in equilibrium with a small quantity of norcaradiene has so far not been clearly answered. The conversion into the bicyclic system that occurs in several reactions cannot be considered as proof of valence tautomerism; the alternative remains that the cyclization is a result of an interaction with the attacking reagent. The same situation is encountered with the Buchner acids and other derivatives of tropilidene [39].

It is interesting to note that cycloheptatriene was recently converted photochemically [43] into its isomer with a cyclobutene structure, *viz.* bicyclo[3,2,0]hepta-2,6-diene mentioned already; this strikingly stable hydrocarbon can be reconverted into tropilidene only at temperatures above 200 °C [43,44].

In view of the uncertainty about the proper electronic structure of cycloheptatriene, information on the spectral properties of the norcaradiene system seemed to be useful to us.

An obvious way of fixing the norcaradiene system is to bridge its carbon atoms 1 and 6 *(33)*. Molecular models show that rearrangement to the corresponding cycloheptatriene *(34)* should be safely blocked by a bridge of three CH_2 groups.



(33) *(34)*

Although the synthesis of *(33)* has not yet been completed, the projected route may be briefly outlined [45]: 4,7-dihydroindane *(35)*, which is readily accessible by Birch reduction of indane [46], was reacted with dibromocarbene, which added selectively [47] to the

[32] *K. Alder* and *G. Jacobs*, Chem. Ber. *86*, 1528 (1953).

[33] *J. C. H. Hwa*, *P. L. de Benneville*, and *H. J. Sims*, J. Amer. chem. Soc. *82*, 2537 (1960).

[34] *W. v. E. Doering* and *W. Roth*, personal communication.

[35] *D. H. R. Barton*, Helv. chim. Acta *42*, 2604 (1959); *R. Srinivasan*, J. Amer. chem. Soc. *82*, 5063 (1960); *83*, 2806 (1961); review of valence isomerizations induced photochemically: *P. de Mayo* and *S. T. Reid*, Quart. Reviews (chem. Soc. London) *15*, 393 (1961).

[36] *R. Willstätter*, Liebigs Ann. Chem. *317*, 204 (1901).

[37] *A. Ladenburg*, Liebigs Ann. Chem. *217*, 74 (1883).

[38] *H. van de Vloed*. Ph.D. Thesis, Universität Marburg 1946; *H. Meerwein*, *H. Disselnkötter*, *F. Rappen*, *H. von Rintelen*, and *H. van de Vloed*, Liebigs Ann. Chem. *604*, 151 (1957).

[39] Literature review: *E. Vogel*, Angew. Chem. *72*, 6 (1960).

[40] *E. J. Corey*, *H. J. Burke*, and *W. A. Remers*, J. Amer. chem. Soc. *77*, 4941 (1955).

[41] *W. v. E. Doering*, *G. Laber*, *R. Vonderwahl*, *N. F. Chamberlain*, and *R. B. Williams*, J. Amer. chem. Soc. *78*, 5448 (1956); *M. V. Evans* and *R. C. Lord*, ibid. *82*, 1876 (1960).

[42] *K. Conrow*, J. Amer. chem. Soc. *83*, 2958 (1961).

[43] *W. G. Dauben* and *R. L. Cargill*, Tetrahedron *12*, 186 (1961).

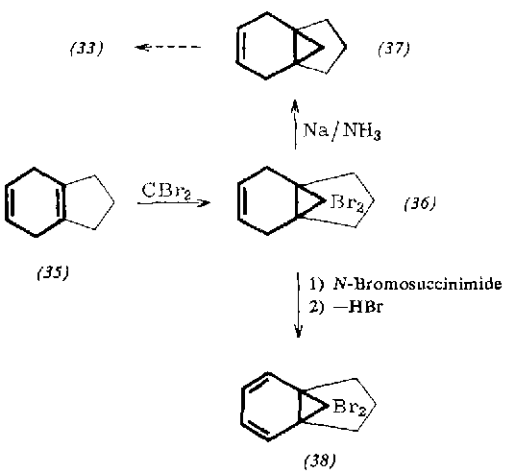
[44] *E. Vogel*, Angew. Chem. *68*, 189 (1956); *M. V. Evans* and *R. C. Lord*, J. Amer. chem. Soc. *83*, 3409 (1961).

[45] Unpublished studies, made together with *W. Wiedemann*.

[46] *E. Giovannini* and *H. Wegmüller*, Helv. chim. Acta *41*, 933 (1958).

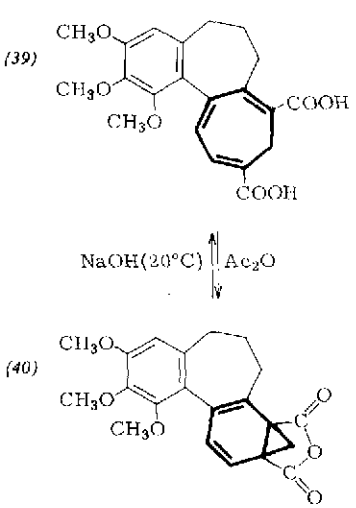
[47] *P. S. Skell* and *A. Y. Garner*, J. Amer. chem. Soc. *78*, 5430 (1956); *W. v. E. Doering* and *W. A. Henderson* jr., ibid. *80*, 5274 (1958).

more nucleophilic tetrasubstituted double bond to give *(36)*. Reduction of the dibromo compound *(36)* with sodium in liquid ammonia[48] furnished the hydrocarbon *(37)* in good yield and in high purity. Attempts to introduce a second double bond into *(37)* have so far always led to mixtures of hydrocarbons. However, these do seem to contain the bridged norcaradiene *(33)*.



The dibromide *(36)* was converted without any difficulty into the norcaradiene derivative *(38)* using *N*-bromosuccinimide. Proof for the structure of *(38)* is based on its nuclear magnetic resonance spectrum and on the result of its catalytic hydrogenation: two moles of hydrogen are taken up, and the same hydrogenation product is formed as from the starting material *(36)*. The ultraviolet spectrum of *(38)* shows two peaks, one at 238 mμ (log ε = 3.72), and the other at 293 mμ (log ε = 3.18). It is uncertain whether this spectrum is typical of the norcaradiene system, since it is difficult to estimate the influence of the bromine atoms on the spectrum.

The formation of a norcaradiene fixed by a bridge has meanwhile also been described by *Eschenmoser* et al. [49]. This group isolated a cycloheptatrienedicarboxylic acid *(39)* in the course of their synthesis of colchicine. On heating with acetic anhydride, compound *(39)* forms the anhydride *(40)*. As was expected, *(40)* reverts to *(39)* on hydrolysis.

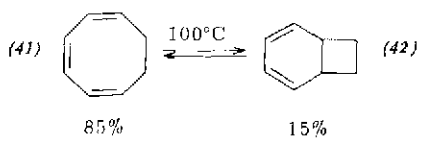


[48] *E. E. Schweizer* and *W. E. Parham*, J. Amer. chem. Soc. *82*, 4085 (1960).

[49] *J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall*, and *A. Eschenmoser*, Helv. chim. Acta *44*, 540 (1961).

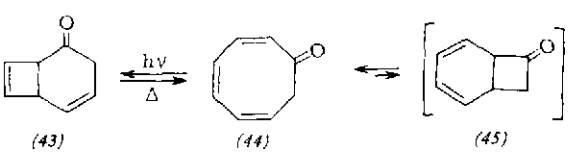
b) The Valence Isomeric System Cycloocta-1,3,5-triene ⇌ Bicyclo[4,2,0]octa-2,4-diene

While an unusual structural problem is encountered in the case of the valence isomeric system cycloheptatriene ⇌ norcaradiene, the relationship is unambiguous in the homologous system cycloocta-1,3,5-triene ⇌ bicyclo-[4,2,0]octa-2,4-diene, which was already mentioned in the introduction; here both hydrocarbons are known. According to studies of *Cope* et al. [1], at 80–100 °C cycloocta-1,3,5-triene *(41)* and bicyclo[4,2,0]octa-2,4-diene are in equilibrium, the ratio of the hydrocarbons being 85:15. Since the free energies of the mono- and bicyclic isomers differ only by very little [ΔF for *(41)* → *(42)* at 100 °C is approximately 1.5 kcal./mole], steric or electronic substituent effects are sufficient to



shift the equilibrium almost completely to one side or the other. Thus, chloro [50], bromo [50], acetoxy [50], or methoxy groups [51] in the 7- or 8-positions stabilize the bicyclo[4,2,0]octa-2,4-diene system. However, bicyclo[4,2,0]octa-2,4-dienes with electronegative substituents in the 1- or 1- and 6-positions rearrange very easily to the eight-membered isomers. This is due to the tendency of the substituents to enter into conjugation with the triene system of the eight-membered ring and to the unfavorable conformation of the two neighboring *cis*-substituents in the four-membered ring. The eight-membered ring is also favored in the case of the isomeric pair bicyclo[4,2,0]octa-2,4-dien-7-one *(45)* and cycloocta-1,3,5-trien-7-one *(44)* [52]. Again, this is probably caused by electronic and steric factors (I strain) [53].

Irradiation of cyclooctatrienone with ultraviolet light produces, as in the case of tropilidene, a valence isomer with a cyclobutene structure *(43)*. This compound reverts to the eight-membered ring ketone on heating [54].



Several years ago, *Alder* and *Dortmann* [55] pointed out the possibility of using the valence isomeric relationship in the bicyclo[4,2,0]octa-2,4-diene ⇌ cycloocta-1,3,5-triene system for the synthesis of eight-membered ring compounds. They

[50] *W. Reppe, O. Schlichting, K. Klager*, and *T. Toepel*, Liebigs Ann. Chem. *560*, 1 (1948); *A. C. Cope* and *M. Burg*, J. Amer. chem. Soc. *74*, 168 (1952).

[51] *H. Meister*, German Patent Application 1 091 563 (Aug. 8th, 1959), Chemische Werke Hüls; cf. Chem. Zbl. *1961*, 2445.

[52] *A. C. Cope* and *B. D. Tiffany*, J. Amer. chem. Soc. *73*, 4158 (1951); *A. C. Cope, S. F. Schaeren*, and *E. R. Trumbull*, ibid. *76*, 1096 (1954).

[53] *H. C. Brown* and *M. Gerstein*, J. Amer. chem. Soc. *72*, 2926 (1950); *H. C. Brown, R. S. Fletcher*, and *R. B. Johannesen*, ibid. *73*, 212 (1951).

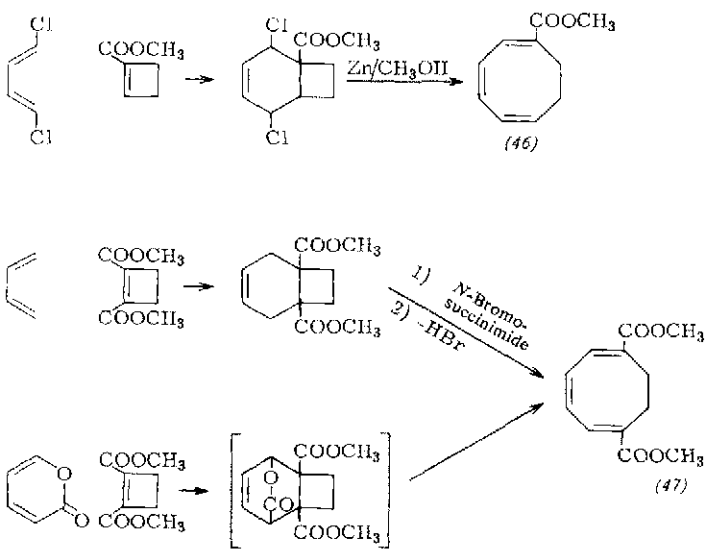
[54] *G. Büchi*, personal communication.

[55] *K. Alder* and *H. A. Dortmann*, Chem. Ber. *87*, 1492 (1954).

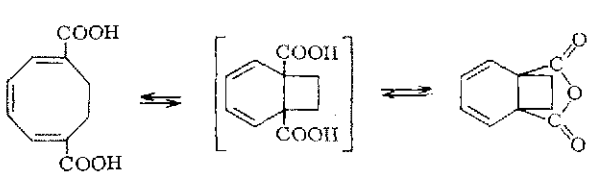
converted the adduct of butadiene and maleic anhydride via several intermediates into bicyclo[4,2,0]octa-2,4-diene, which on heating isomerized to cycloocta-1,3,5-triene. Several 1-cyanobicyclo[4,2,0]octa-2,4-dienes are accessible by photochemical addition of ethylene derivatives onto benzonitrile, according to *Ayer* and *Büchi* [56]. Of these compounds, however, only the adduct of vinylacetate and benzonitrile seems to have been thermally isomerized, whereby a mixture of 1-cyanobicyclo[4,2,0]octa-2,4,7-triene and the valence isomeric cyanocyclooctatetraene was formed. With bicyclo-[4,2,0]octa-2,4-dienes [57], which are formed by photochemical addition of maleic anhydride onto benzene and other aromatic hydrocarbons, rearrangement to the eight-membered ring cannot occur because the bicyclic compounds immediately add on a second molecule of maleic anhydride.

A new way for the preparation of cycloocta-1,3,5-trienes was opened up by our observation that dimethyl cyclobutene-1,2-dicarboxylate and other cyclobutenes with an activated double bond are excellent dienophiles which add onto 1,3-dienes forming bicyclo[4,2,0]octa-3-enes in high yields. In an attempt to convert the bicyclo-[4,2,0]octa-3-enes into bicyclo[4,2,0]octa-2,4-dienes, the isomeric eight-membered ring compounds were obtained directly [58].

The method may be illustrated by the syntheses of methyl cycloocta-1,3,5-triene-1-carboxylate *(46)* and dimethyl cycloocta-1,3,5-triene-1,6-dicarboxylate *(47)* [58].

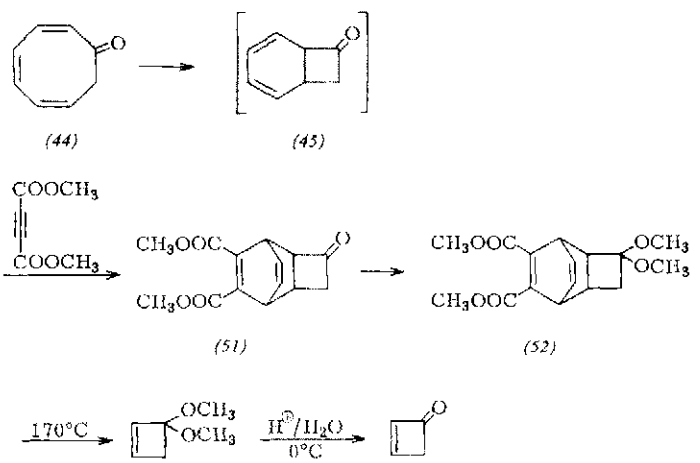


We may assume that *(46)* and *(47)* and their corresponding acids are, at least at higher temperatures, in equilibrium with small amounts of their bicyclic isomers. It has been possible, in the case of cycloocta-1,3,5-triene-1,6-dicarboxylic acid *(48)*, to trap the isomeric bicyclic acid *(49)* by anhydride formation when *(48)* was heated with acetic anhydride. However, *(49)* could not be isolated on careful hydrolysis of the anhydride. The eight-membered ring acid *(48)* was reverted quantitatively even when *(50)* was hydrolyzed at room temperature.



Employing the valence isomeric relationship between the cyclooctatriene- and bicyclo[4,2,0]octadiene system one can not only transform four-membered ring compounds into eight-membered ring compounds as shown by examples of the syntheses of cyclooctatriene-carboxylic esters, but conversely eight-membered ring compounds can be converted into four-membered ring compounds.

Following this synthetic approach, we were able to prepare cyclobutenone [59], which has otherwise not been accessible up to the present. This substance deserves attention in connection with the cyclobutadiene problem [60].



Cyclooctatrienone *(44)*, which can be obtained readily from cyclooctatetraene reacted with dimethyl acetylenedicarboxylate in its valence-isomeric bicyclic structure *(45)* to give the adduct *(51)*. According to the rule of *Alder* and *Rickert*, compound *(51)* should decompose on heating into cyclobutenone and dimethyl phthalate. Owing to the instability of the cyclobutenone, thermal cleavage yielded only polymerization products of the ketone. If, however, the adduct is first converted into its dimethyl ketal *(52)* and the latter is then subjected to pyrolysis, a good yield of the dimethyl ketal of cyclobutenone, which is thermally more stable is obtained. Careful hydrolysis of the ketal at 0 °C yields the extremely unstable cyclobutenone.

Addition of carbenes onto cyclooctatetraene [61] leads to a series of interesting bicyclic cyclooctatriene derivatives, *viz.* bicyclo[6,1,0]nona-2,4,6-trienes *(53)*. For compounds of this type various possibilities of isomerization can be envisaged. First they might cyclize in the familiar way to give the tricyclic valence isomers *(54)* although one would guess that the strain inherent in these structures renders their formation not very likely. As

[56] *D. E. Ayer* and *G. Büchi*, Amer. Pat. 2805242 (Sept. 3rd, 1957), E. I. du Pont de Nemours & Co.; cf. Chem. Abstr. *52*, 2904 (1958).

[57] *H. J. F. Angus* and *D. Bryce-Smith*, Proc. chem. Soc. (London) *1959*, 326; J. chem. Soc. (London) *1960*, 4791; *G. O. Schenck* and *R. Steinmetz*, Tetrahedron Letters *1960*, No. 21, p. 1.

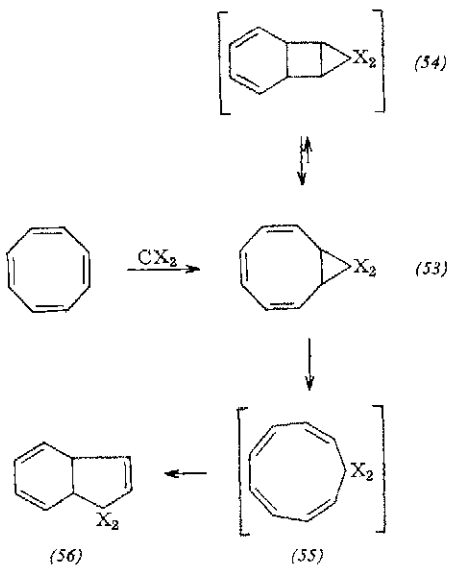
[58] *E. Vogel*, *O. Roos*, and *K. H. Disch*, Liebigs Ann. Chem. *653*, 55 (1962); *G. Wendt*, Diploma Thesis, Universität Köln 1962.

[59] *E. Vogel* and *K. Hasse*, Liebigs Ann. Chem. *615*, 22 (1958), as well as unpublished studies made together with *K. Hasse*.

[60] *W. Baker* and *J. F. W. McOmie* in *D. Ginsburg*: Non-Benzenoid Aromatic Compounds Interscience, New York 1959, p. 43.

[61] *E. Vogel* and *H. Kiefer*, Angew. Chem. *73*, 548 (1961).

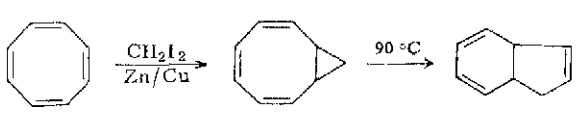
vinylogues of norcaradiene, they should be expected to undergo ring expansion readily to form cyclononatetraenes *(55)*. It should be difficult to demonstrate the formation of (and even more difficult to isolate) such cyclononatetraenes, since these compounds are presumably very reactive owing to the presence of angle-strained double bonds and become stabilized by spontaneous cyclization to 8,9-dihydroindenes *(56)*.



(54) *(53)* *(56)* *(55)*

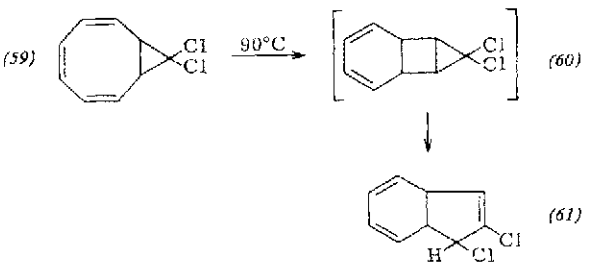
It is also possible that the adducts of cyclooctatetraene and carbenes are transformed into 8,9-dihydroindenes without going through the nine-membered ring intermediates.

Transfer of the methylene group onto cyclooctatetraene can best be achieved with methylene iodide and a zinc/copper couple (iodomethylzinc iodide) according to *Simmons* and *Smith* [62], because, in contrast to the photochemical or CuCl-catalysed reaction with diazomethane, no interfering by-products are formed. The crystalline hydrocarbon, isolated in low yield, was identified as bicyclo[6,1,0]nona-2,4,6-triene *(57)* by its nuclear magnetic resonance spectrum and its chemical properties. As anticipated, the compound is thermally labile; it is converted into a liquid isomer even at 90 °C. However, this isomer is not cyclononatetraene but 8,9-dihydroindene *(58)*, a compound known previously [63]. Studies of the mechanism of this rearrangement are still in progress.



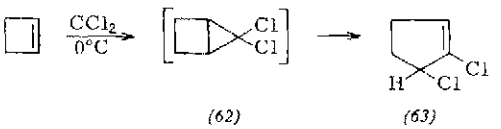
(57) *(58)*

Dichlorocarbene, which can be prepared by various procedures, adds very easily onto cyclooctatetraene to form 9,9-dichlorobicyclo[6,1,0]nona-2,4,6-triene in good yield *(59)*. Similar to the hydrocarbon, the dichlorocarbene adduct rearranges on heating to only 80–90 °C. The isomer formed in almost quantitative yield was ascribed the dihydroindene structure *(61)*, with vicinal chlorine atoms. It appears to be sterically uniform.



(59) *(60)* *(61)*

The rearrangement of *(59)* to *(61)* is undoubtedly related to the isomerization observed recently [64] with other cyclopropane derivatives with geminal halogen substituents. Thus, on being heated briefly to 155 °C, 6,6-dibromobicyclo-[3,1,0]hexane [65], is converted into 2,3-dibromocyclohexene while 5,5-dichlorobicyclo[2,1,0]pentane *(62)*, made from dichlorocarbene and cyclobutene, apparently rearranges even in the nascent state at 0 °C to 2,3-dichlorocyclopentene *(63)* [66].



(62) *(63)*

Judging from the instability of *(62)* and the several examples of reversible rearrangements of cycloocta-1,3,5-trienes to bicyclo[4,2,0]octa-2,4-dienes, we assume that the rearrangement of the cyclooctatetraene dichlorocarbene adduct *(59)* proceeds via the tricyclic isomer *(60)*. The latter contains the bicyclo[2,1,0]pentane system with geminal chlorine atoms as a structural element. Whether ionic intermediates are involved when the three-membered ring in *(59–60)* opens or whether ring opening and migration of the halogen atom occur concertedly without appreciable charge separation has not yet been established. It may be mentioned in this connection that *(59)* does not undergo solvolysis at room temperature and is inert towards an aqueous alcoholic solution of silver nitrate.

The same rearrangement as observed for *(59)* has also been found for the adduct of dibromocarbene to cycloocta-tetraene.

c) The Valence Isomeric System Cyclonona-1,3,5-triene ⇌ Bicyclo[4,3,0]nona-2,4-diene

The mobility that distinguishes the two valence isomeric systems discussed above does not extend to the homologous system cyclonona-1,3,5-triene ⇌ bicyclo-[4,3,0]nona-2,4-diene [67].

Both *cis*- and *trans*-bicyclo[4,3,0]nona-2,4-diene lack ring strain as a driving force for the rearrangement. They are therefore stable. Whether these hydrocarbons partly isomerize to cyclononatrienes at higher temperatures is not clear yet. According to *Alder* and *Dortmann* [67], Hofmann degradation of α-des(dimethyl)homogranatenine *(64)* (both double bonds have the *cis*-configuration) yields primarily *cis,cis,trans*-cyclonona-1,3,5-triene

[62] *H. E. Simmons* and *R. D. Smith*, J. Amer. chem. Soc. *80*, 5323 (1958); *81*, 4256 (1959); *G. Wittig* and *K. Schwarzenbach*, Liebigs Ann. Chem. *650*, 1 (1961).

[63] *K. Alder* and *F. H. Flock*, Chem. Ber. *87*, 1916 (1954).

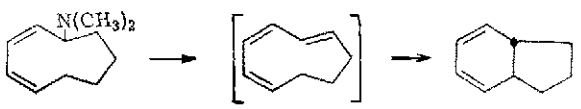
[64] Literature review: *E. Vogel*, Angew. Chem. *72*, 8 (1960).

[65] *J. Sonnenberg* and *S. Winstein*, J. org. Chemistry *27*, 748 (1962).

[66] Unpublished studies, made together with *H. Kiefer*.

[67] *K. Alder* and *H. A. Dortmann*, Chem. Ber. *87*, 1905 (1954).

(65). This immediately cyclizes to the more stable bicyclic isomer, *trans*-bicyclo[4,3,0]nona-2,4-diene *(66)*. The assumption that the minor modification of hydrocarbon *(66)* that occurs upon heating it to 120 °C is due to partial isomerization to cyclononatriene requires reinvestigation. The valence isomerization of *(65)* to *(66)* also does not seem to be firmly established, since Hofmann elimination with *(64)* may possibly proceed in a transannular fashion and lead directly to *(66)*.



(64) *(65)* *(66)*

Thus, we find qualitatively the same stability relationships in the valence-isomeric systems cycloheptatriene ⇌ norcaradiene, cycloocta-1,3,5-triene ⇌ bicyclo[4,2,0]-octa-2,4-diene, and cyclonona-1,3,5-triene ⇌ bicyclo-[4,3,0]nona-2,4-diene, as in the homologous series of the *cis*-1,2-divinylcycloalkanes.

Similar to cyclononatriene and cyclononatetraene, ten-membered cyclic polyenes with three or more conjugated double bonds seem to be very unstable compounds [68]. Of these (as yet unknown) hydrocarbons, cyclodecapentaene deserves special attention, being the higher vinylogue of benzene and cyclooctatetraene. Though *Hückel*'s rule [69] predicts aromatic character for cyclodecapentaene, in all probability the hydrocarbon has the properties of a polyolefin, since it cannot attain a planar configuration without imposing unduly high strain on the molecule. Presumably,

cyclodecapentaene undergoes a valence isomerization under the conditions of its formation to give 9,10-dihydronaphthalene (or other isomers), a rearrangement for which a precedence has recently been discovered [70].

Received, Aug. 14th, 1962 [A 235/64 IE]

[68] A cyclodecatriene is probably an intermediate in the photochemical epimerization of isodehydrocholesterol to $\Delta^{6,8}$-coprostadienol: *A. Windaus, L. Linsert*, and *H. J. Eckhardt*, Liebigs Ann. Chem. *534*, 22 (1938); *A. Windaus* and *G. Zühlsdorff*, ibid. *536*, 204 (1938).

[69] *E. Hückel*, Z. Physik *70*, 204 (1931).

[70] *M. Avram, C. D. Nenitzescu*, and *E. Marica*, Chem. Ber. *90*, 1857 (1957).

Stereochemistry of Displacement Reactions at Phosphorus Atoms

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Recent interest in the stereochemistry of displacement reactions involving second row elements has led to rapid advances in the preparation and resolution of asymmetric phosphorus compounds. The changes in optical activity accompanying substitution at an optically active phosphorus atom, the reactivity of cyclic phosphates, and the mechanism of intramolecular decomposition reactions involving a phosphorus centre are discussed in terms of the electronic structure of possible transition states.

1. Synthesis of Optically Active Phosphorus Compounds

Stereochemical changes accompanying chemical reactions are closely related to the corresponding changes in optical activity, and consequently there has been renewed interest in recent years in the preparation and optical resolution of compounds containing an asymmetric phosphorus atom. The classical work of *Meisenheimer* [1] showed for the first time that optically active phosphorus compounds are stable, and subsequently phosphine sulfides [2], phosphonium, and spirocyclic phosphonium salts [3] were resolved. At the present time, simple and efficient methods have been developed to resolve phosphoryl compounds [4] and phosphonium

[1a] *J. Meisenheimer* and *L. Lichtenstadt*, Ber. dtsch. chem. Ges. *44*, 356 (1911).

[1b] *J. Meisenheimer, J. Casper, M. Höring, W. Lauter, L. Lichtenstadt* and *J. Samuel*, Liebigs Ann. Chem. *449*, 213 (1926).

[2] *W. C. Davies* and *F. G. Mann*, J. chem. Soc. (London) *1944*, 276.

[3a] *F. G. Holliman* and *F. G. Mann*, J. chem. Soc. (London), *1947*, 1634.

[3b] *F. A. Hart* and *F. G. Mann*, J. chem. Soc. (London) *1955*, 4107.

[4a] *D. M. Coyne, W. E. McEwen*, and *C. A. VanderWerf*, J. Amer. chem. Soc. *78*, 3061 (1956).

[4b] *K. L. Marsi, C. A. VanderWerf*, and *W. E. McEwen*, J. Amer. chem. Soc. *78*, 3063 (1956).

[4c] *G. Hilgetag* and *G. Lehmann*, J. prakt. Chem. *8*, 224 (1959).

[4d] *G. Hilgetag* and *G. Lehmann*, J. prakt. Chem. *9*, 3 (1959).

[4e] *M. Green* and *R. F. Hudson*, J. chem. Soc. (London) *1958*, 3129.

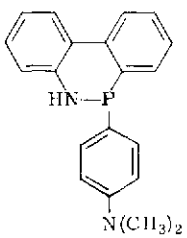
[4f] *M. Green* and *R. F. Hudson*, Proc. chem. Soc. (London) *1961*, 145.

[4g] *H. S. Aaron, T. M. Shryne*, and *J. I. Miller*, J. Amer. chem. Soc. *80*, 107 (1958).

[4h] *H. S. Aaron, J. Braun, T. M. Shryne, H. F. Frack, G. E. Smith, R. T. Uyeda*, and *J. I. Miller*, J. Amer. chem. Soc. *82*, 596 (1960).

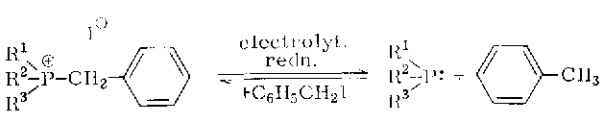
salts [5], thus enabling investigations to be made on the stereochemistry of substitution at these centres.

Whereas the optical stability of these compounds is well established, it was thought until quite recently that optically active phosphines would racemize rapidly at room temperature. Thus, *Weston* [6] calculated the potential energy barrier for inversion of the pyramidal structure from a potential energy function derived from vibrational frequencies and molecular dimensions. The following inversion times were found: NH_3, $2.5 \cdot 10^{-11}$ sec; PH_3, 2.3×10^{-6} sec; AsH_3, 1.4 years; and $(H_3C)_3P$, 2 hours. It has recently been found, however, that phosphines are considerably more optically stable than predicted by these values. Thus *(1)* can be resolved into its enantiomorphs [7] and is optically stable. Here the activity may be due to puckering of the molecular framework, *i.e.* dissymmetry.



(1)

However, *Horner* et al. [8] have prepared several optically active phosphines by electrolytic reduction of the corresponding benzylphosphonium salts *(2)*.

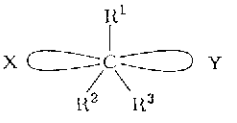


(2) (+) (+)

(+)-Methyl-n-propylphenylphosphine racemizes very slowly in boiling toluene, the activation energy being in the region of 25 kcal/mole [9]. Treatment of the active phosphine with benzyl iodide in a reaction which does not involve displacement at phosphorus gave the phosphonium salt with the original configuration. This suggests that the reduction proceeds by nucleophilic interaction [10] of the cathode with the α-carbon atom of the benzyl group according to an S_N2 mechanism.

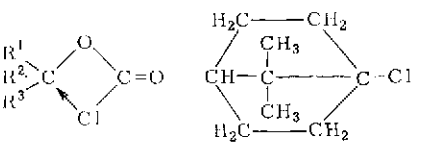
2. Displacement Reactions at First and Second Row Elements

Extensive investigations of the stereochemical changes accompanying substitution at saturated carbon atoms have led to very simple orientation rules. Thus, bimolecular substitution invariably leads to inversion of configuration [11]. Theoretically, this result may be ascribed to the use of a lone 2p orbital to bind the incoming and outgoing groups *(3)*, the other orbitals of carbon lying too high to participate in effective bonding.



(3)

However, some unimolecular re-arrangements, particularly thermal decomposition of chloroformates, do proceed with retention of configuration [12]. This suggests that a cyclic transition state *(4)* may be formed (S_Ni), although the intermediate formation of ion-pairs is widely postulated.



(4) *(5)*

Although the bonding in *(4)* is difficult to describe, the existence [13] of molecules with bridging methyl groups, *e.g.* dimethylberyllium $[Be(CH_3)_2]_n$ and trimethylaluminum, shows that configurations other than *(3)* are possible. Transition states in which the configuration is retained are energetically unfavorable, however, as is shown by the stability of the bridgehead compound *(5)* towards nucleophilic reagents [14].

With second row elements, the position is more complex in view of the increased stability of the higher valency states. This is normally attributed to interaction of 3d orbitals, hybridisation with which leads to a range of possible structures. It should be noted, however, that the energy levels of the 3d orbitals are very high, and the higher valency states may be stabilized entirely by electrostatic forces, as suggested by *Pauling* [15]. The increased coordination number is then attributed to the increased radius.

Substitution at a silicon atom [16] proceeds at comparable rates with inversion or retention of configuration and displacement reactions have been observed to proceed rapidly at bridgehead silicon atoms. As with carbon and silicon, the electronic distribution in 3- and 4-coordinated phosphorus compounds is approximately tetrahedral. Addition of a nucleophile to give an intermediate (or transition state) with 10 electrons around the central phosphorus atom is therefore subject to the same stereochemical control as nucleophilic substitution at carbon and silicon.

[5] *K. F. Kumli, W. E. McEwen,* and *C. A. VanderWerf,* J. Amer. chem. Soc. *81*, 248 (1959).

[6] *R. E. Weston,* J. Amer. chem. Soc. *76*, 2645 (1954).

[7] *I. G. M. Campbell* and *J. K. Way,* J. chem. Soc. (London) *1960*, 5034.

[8] *L. Horner, H. Winkler, A. Rapp, A. Mentrup, H. Hoffmann,* and *P. Beck,* Tetrahedron Letters No. 5, 161 (1961).

[9] *L. Horner,* personal communication.

[10] *G. Klopman,* Helv. chim. Acta *54*, 1908 (1961).

[11] *C. K. Ingold:* Structure and Mechanism in Organic Chemistry. G. Bell, London 1953, p. 372.

[12a] *A. H. J. Houssa* and *H. Phillips,* J. chem. Soc. (London) *108*, 1232 (1932).

[12b] *K. B. Wiberg* and *T. M. Shryne,* J. Amer. chem. Soc. *77*, 2774 (1955).

[13] *H. C. Longuet-Higgins,* Quart. Reviews *11*, 121 (1957).

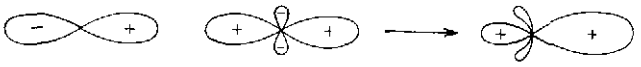
[14] *D. P. Bartlett* and *L. H. Knox,* J. Amer. chem. Soc. *61*, 3184 (1939).

[15] *L. Pauling:* Nature of the Chemical Bond. 1st Ed., Cornell University Press, Ithaca 1940, p. 232.

[16] *L. H. Sommer,* Angew. Chem. internat. Edit. *1*, 143 (1962).

3. Electronic Structures of PX_5 Molecules and Transition States

Electronically, several structures are possible, depending on the particular d-orbital used for hybridization. Thus, hybridization of the d_{z^2} orbital with the p_z orbital leads to two pd orbitals *(6)*.



The two pd bonds together with three sp^2 bonds lead to a bipyramidal structure *(7)*, which has been established for PF_5, PCl_5, PCl_3F_2, and PBr_5 in the gas phase [17]. Whereas the bonds in tetrahedral and octahedral complexes are equivalent, those in a bipyramidal molecule are not necessarily so, and three situations may arise;

a) For pd-sp^2 hybridisation, the axial pd bonds will be longer and weaker than the radial bonds. Hence a transition state with this structure would be similar to an S_N2 transition state giving inversion of configuration.

b) Re-hybridisation to give five sp^3d bonds with equal energies is possible, and *Craig* et al. [18] have shown that the overlap integrals, and by analogy the bond strengths, are the same for a structure in which the axial bonds are slightly longer than the radial bonds. A transition state of this kind would presumably racemize, since retention and inversion are equally probable.

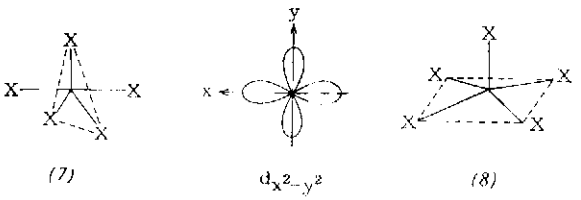
c) It is possible that in an sp^3d hybridized structure the radial bonds are actually weaker than the axial bonds, as shown by the calculations of *Duffey* [19], and this is supported to some extent by the ready replacement of 3 of the chlorine atoms in PCl_5 by radioactive chlorine [20].

$$PCl_5 + 3\,Cl^* \rightarrow PCl_3^*Cl_2 + 3\,Cl$$

A displacement involving the radial bonds only would give rise to inversion of configuration, as suggested recently by *Haake* and *Westheimer* [21].

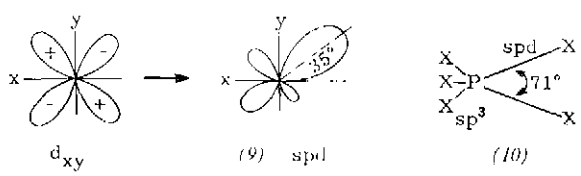
It is seen therefore that a bipyramidal transition state may lead to several alternative stereochemical courses, and it is perhaps useful to classify them by using the following hypothesis. Since the 5-coordinated state (assuming participation of 3d orbitals) is stabilized by the positive charge [*] on the phosphorus atom, structure (a) is expected when this charge is small, and structure (b) and (c) when it is large. The application of this hypothesis is discussed in Section 6.

Hybridizations with other d orbitals lead to other structures. Thus $d_{x^2-y^2}p_xp_ys$ hybridization leads to a planar square structure. Use of a further p orbital gives a square pyramidal structure *(8)*.

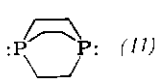


Non-bonded repulsions are greater in *(8)* than in *(7)*, but the energy difference could be overcome by an increase in d_π-p_π bonding, if the groups X are capable of conjugation. Recently [22], $Sb(C_6H_5)_5$ has been shown to have this structure *(8)* in the solid state with the antimony atom approximately 0.5 Å above the basal plane, and a similar structure is considered for $P(C_6H_5)_5$ and $As(C_6H_5)_5$. With these compounds, the particular structure may be stabilized by crystal forces, but this shows at least that structures other than the bipyramidal form *(7)* are energetically possible. A transition state of structure *(8)* would lead to retention of configuration.

Hybridization of an sp^3 orbital with the d_{xy} orbital *(9)* gives a structure *(10)* with an angle of 71 ° between the two spd bonds [23].



A transition state with this structure is probably involved in reactions at bridgehead silicon atoms. Unfortunately no reactions have so far been reported at bridgehead phosphorus atoms, although several attempts have been made to prepare suitable compounds, and *Mann* [24] has reported the preparation of 1,4-diphosphabicyclo[2,2,2]octane *(11)*.



It is apparent therefore from this brief discussion that a wide range of transition states for substitution at phosphorus atoms is possible; this is reflected in the various types of reactions described in the following sections.

4. Phosphines and Phosphonium Salts

The availability of optically active phosphines has enabled the reactions described in Scheme 1 to be performed [8].

By making the reasonable assumption that the quaternization and oxidation reactions which do not involve

[17] Interatomic Distances. Chem. Soc. Special Publication No. 11, London 1958, p. M 54 and M 55.

[18a] *D. P. Craig, A. Maccoll, R. S. Nyholm, L. E. Orgel*, and *L. E. Sutton*, J. chem. Soc. (London) *1954*, 332.

[18b] *H. H. Jaffé*, J. chem. Physics *21*, 258 (1953).

[19] *G. H. Duffey*, J. chem. Physics *17*, 196 (1949).

[20] *J. Downs* and *R. E. Johnson*, J. chem. Physics *22*, 143 (1954).

[21] *P. C. Haake* and *F. H. Westheimer*, J. Amer. chem. Soc. *83*, 1102 (1961).

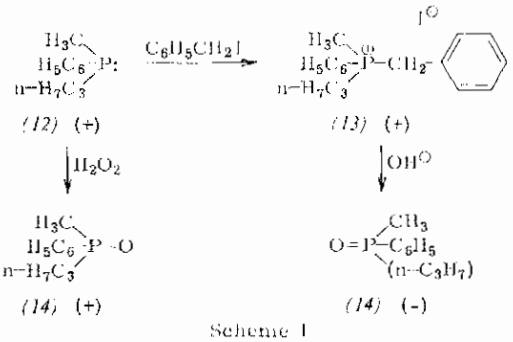
[*] induced by electronegative groups.

[22] *P. J. Wheatley* and *G. Wittig*, Proc. chem. Soc. (London) *1962*, 251.

[23] *R. J. Gillespie*, J. chem. Soc. (London) *1952*, 1002.

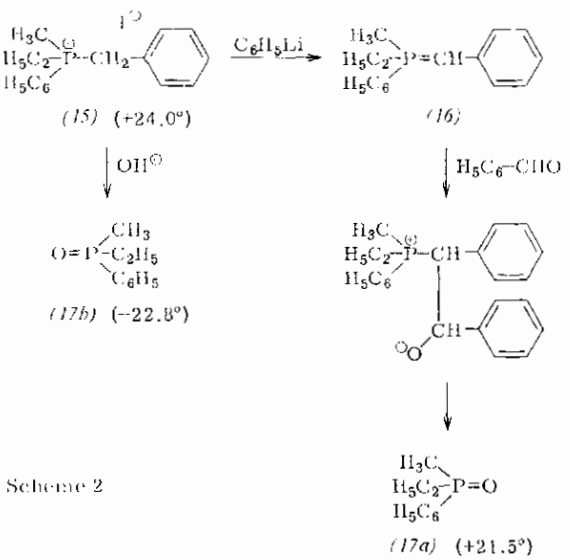
[24] *R. C. Hinton* and *F. G. Mann*, J. chem. Soc. (London) *1959*, 2835.

displacement on phosphorus proceed with retention of configuration, it follows that the methyl-n-propylphenylbenzylphosphonium ion *(13)* reacts stereospecifically



Scheme 1

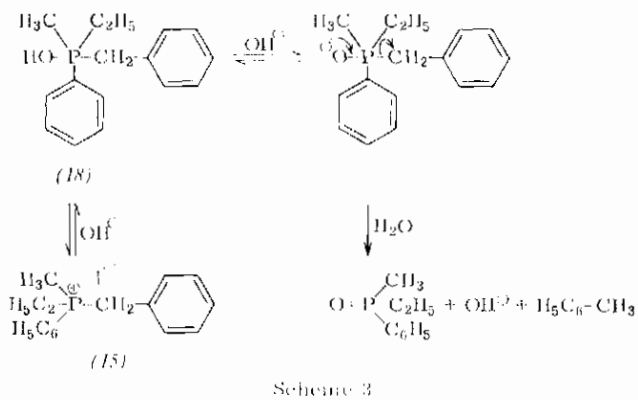
with sodium hydroxide to give methyl-n-propylphenylphosphine oxide *(14)* with inversion of configuration. *VanderWerf* et al. [5] resolved methylethylphenylbenzylphosphonium iodide *(15)* into its enantiomorphs by way of the D(−)- and L(+)-dibenzoyl hydrogen tartrate salts. The optically active phosphorane *(16)* was prepared by treatment of *(15)* with phenyl-lithium and converted into the phosphine oxide *(17a)* by reaction with benzaldehyde [25].



Scheme 2

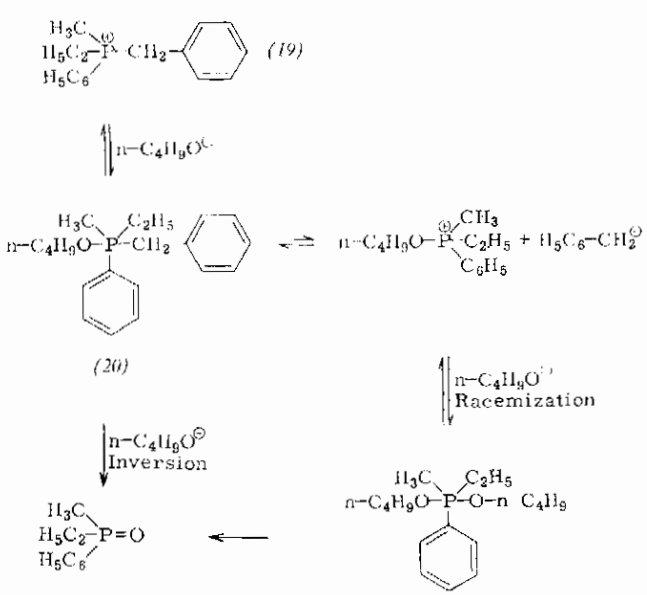
The phosphine oxide *(17b)* was then prepared [26] by the direct action of sodium hydroxide on the phosphonium iodide *(15)* as in Scheme 1. The changes in optical activity shown in Scheme 2 demonstrate clearly that both inversion and retention can occur stereospecifically at a positively charged phosphorus atom. By combining Schemes 1 and 2, it follows that the reaction between the phosphorane *(16)* and the aldehyde proceeds through a cyclic transition state with retention of configuration.

The reaction between phosphonium salts and hydroxide ions has been shown to be of the third order, with a second order dependence on the concentration of sodium hydroxide [27]. A mechanism consistent with the stereochemical and kinetic observations involves a trigonal bipyramidal intermediate *(18)*, which loses a proton reversibly to give the conjugate base. This releases a benzyl ion, which in the presence of water gives toluene. As discussed in Section 3, the observed inversion of configuration does not necessarily mean that the oxygen atom, benzyl group, and phosphorus atom are collinear, since displacement in the radial plane with these groups mutually inclined at 120° would result in the same stereochemical change.



Scheme 3

Further evidence for the existence of a pentacovalent intermediate has been obtained [28] from a study of the stereochemical changes accompanying the decomposition of optically active methylethylphenylphosphonium butoxide *(19)*. According to *Grayson* and *Keough* [29], phosphonium alkoxides of the type $[R_3PCH_2C_6H_5]^+ R'O^-$ are decomposed by alcoholic sodium alkoxide to toluene, phosphine oxide and the ether R′OR′. When an optically active phosphonium salt is used in this reaction, the phosphine oxide produced is highly racemic, suggesting that at some stage a 5-coordinated intermediate is formed. As discussed in Section 3, such an intermediate would be racemic if all the sp^3d bonds were



Scheme 4

[25] *A. Bladé-Font, C. A. VanderWerf,* and *W. E. McEwen,* J. Amer. chem. Soc. *82*, 2396 (1960).

[26] *K. F. Kumli, C. A. VanderWerf,* and *W. E. McEwen,* J. Amer. chem. Soc. *81*, 3805 (1959).

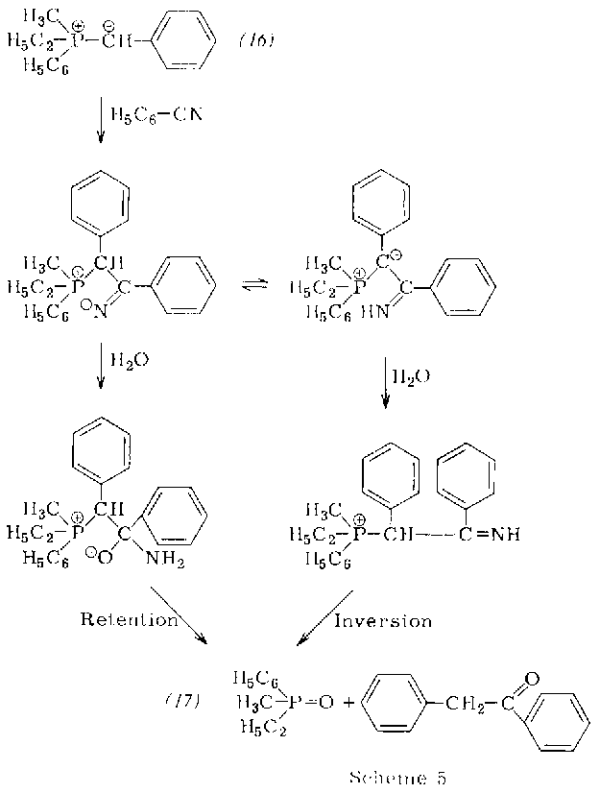
[27] *M. Zanger, C. A. VanderWerf,* and *W. E. McEwen,* J. Amer. chem. Soc. *81*, 3806 (1959).

[28] *C. B. Parisek, C. A. VanderWerf,* and *W. E. McEwen,* J. Amer. chem. Soc. *82*, 5503 (1960).

[29] *M. Grayson* and *P. T. Keough,* J. Amer. chem. Soc. *82*, 3919 (1960).

equivalent. The more complex Scheme 4 was proposed by *McEwen* and *VanderWerf* [28].

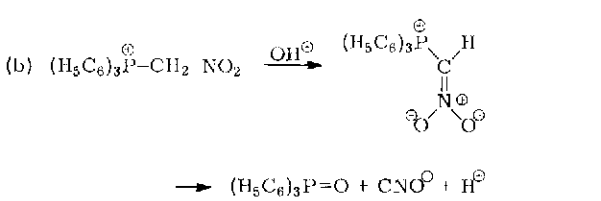
Reaction between the optically active phosphorane *(16)* and benzonitrile gave an orange colored intermediate, which on treatment with aqueous alkali gave the optically active phosphine oxide *(17)* and deoxybenzoin [30]. The relative configurations of *(16)* and *(17)* having been established, measurement of the activity of the phosphine oxide showed that the reaction proceeds with 68 % inversion, showing that two reaction paths are involved, one involving inversion, and the other retention of configuration.



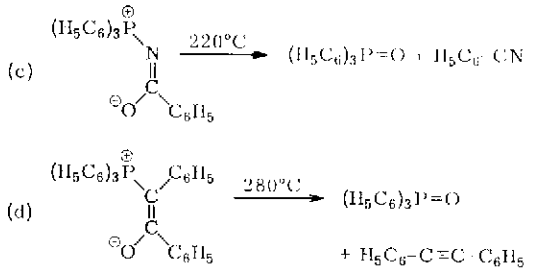
Scheme 5

Recently, the optically active phosphorane *(16)* was treated with styrene oxide to give *(17)* (in 12 % yield), with 50 % inversion of configuration, again showing the occurrence of two different stereochemical processes [31].

Intramolecular rearrangements probably involving cyclic intermediates are common in phosphorus chemistry, and the following additional examples may be quoted. Addition of sodium hydroxide to an α-nitromethyl phosphonium salt gives the phosphine oxide [32], presumably by the following mechanism:



Similarly, phosphonium betaines decompose on pyrolysis [33,34]:

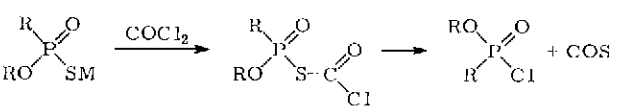


5. Phosphorylation

The biochemical importance of phosphorylation adds further to the interest in the stereochemistry of these reactions, although here progress has been somewhat slower, mainly because of the ease of racemization. This casts doubt on the optical purity of some of the intermediates. The ease of racemization in these systems is not due to spontaneous inversion of the tetrahedral structure, but to traces of impurities when highly reactive compounds, *e.g.* fluorides and chlorides, are used.

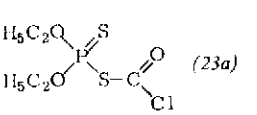
a) Chlorides

Resolution [35] of alkylphosphonothiolic acid *O*-alkyl esters *(21*; M = H) has led to their investigation as possible starting materials for stereospecific routes to other optically active phosphorus compounds. The optically active sodium salts of the acids *(21*; M = Na) were shown to react with carbonyl chloride under mild conditions to give optically active phosphonochloridates *(22)* [35]. The stereochemical course of this reaction was found to be independent of the nature of the solvent.



(21) *(23)* *(22)*

It is interesting that the phosphonochloridate *(22)*, and not the phosphonochloridothionate is formed, suggesting that the reaction proceeds via the intermediate *(23)*. A similar intermediate *(23a)* has recently been isolated



(23a)

from the reaction of potassium *O,O*-diethylphosphonothiolothionate with phosgene [36].

[30] *A. Bladé-Font, C. A. VanderWerf,* and *W. E. McEwen,* J. Amer. chem. Soc. *82,* 2646 (1960).

[31] *W. E. McEwen, A. Bladé-Font,* and *C. A. VanderWerf,* J. Amer. chem. Soc. *84,* 677 (1962).

[32] *S. Trippett* and *D. M. Walker,* J. chem. Soc. (London) *1959,* 3874.

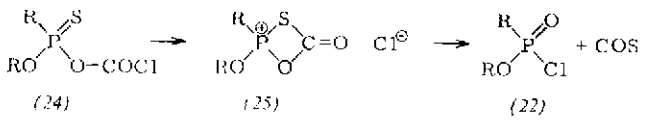
[33] *H. Staudinger* and *E. Hauser,* Helv. chim. Acta *4,* 861 (1921).

[34] *S. Trippett* and *S. T. D. Gough,* J. chem. Soc. (London) *1962,* 2333.

[35] *H. S. Aaron, R. T. Uyeda, H. F. Frack,* and *J. I. Miller,* J. Amer. chem. Soc. *84,* 617 (1962).

[36] *J. I. G. Cadogan,* J. chem. Soc. (London) *1961,* 3067.

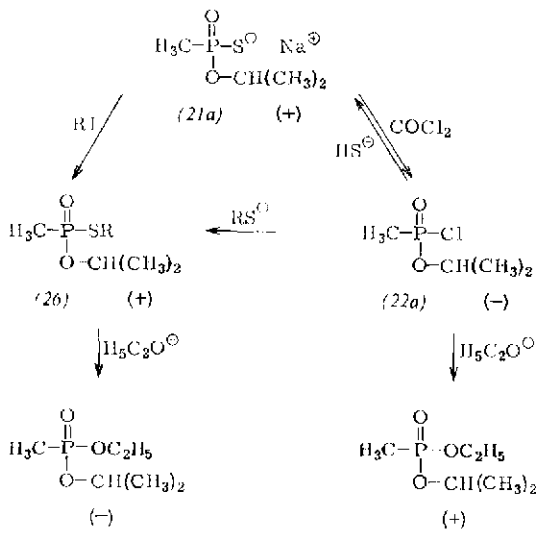
However, reactions of phosphonothioate salts with acetyl chloride and phosphoryl chlorides give *O*-acylation and *O*-phosphorylation, respectively. It has been suggested that the salts of phosphonothioic acids react with phosgene to give the intermediate *(24)*, which cyclizes to *(25)* before decomposing into the phosphonochloridate [35].



(24) *(25)* *(22)*

It is of interest that recent work using ^{18}O as a tracer has shown the absence of a similar cyclic intermediate in the analogous reaction of phosgene with a phosphinate [37].

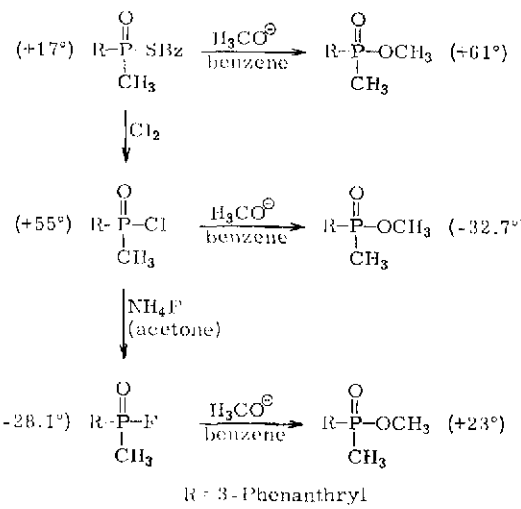
The availability of the chloridates *(22)* in an optically active form has led to a study of the sterochemistry of some nucleophilic displacements at asymmetric phosphoryl centres [35].



Scheme 6

By assuming that the two displacements involving ethoxide ion proceed with the same stereochemical change, the phosphonothiolate *(26)* and phosphonochloridate *(22a)* must have opposite configurations, and therefore the reaction of alkylthioxide ion with the phosphonochloridate *(22a)* proceeds with predominant inversion of configuration. Since alkylation of the sodium salt of the phosphonothiolic acid *(21a)* must proceed with retention of configuration, the reaction between sodium *O*-isopropylmethylphosphonothiolate and phosgene must also proceed with inversion of configuration. The products of all these reactions were not optically pure, so that the importance of a retention mechanism in these reactions cannot be ascertained.

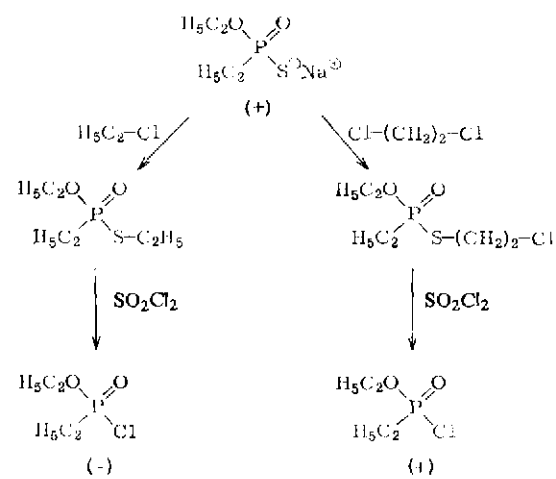
A similar series of displacements (Scheme 7) has been reported [38], using (−)-*S*-benzyl 3-phenanthrylmethylphosphinothiolate, which was resolved [4e] into its enantiomorphs by complex formation with optically active α-(2,4,5,7-tetranitro-9-fluorenylideneamino-oxy)propionic acid.



Scheme 7

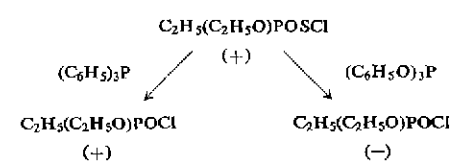
By making the reasonable assumption that reactions between anions and the phosphinic derivatives involve the same stereochemical change, it follows that all these reactions proceed with inversion of configuration. However, no definite conclusions could be drawn, as the products of reaction were not isolated owing to racemization and decomposition on distillation. Nevertheless, these and similar observations provided a basis for more complete studies and drew attention in particular to the necessity of using less reactive intermediates (see Section 5b).

The general assumption underlying Schemes 6 and 7 that similar reactions proceed with similar stereochemical changes, must be used with caution. *Michalski* and *Ratajczak* [39] have shown that both (+)- and (−)-forms of ethylphosphonochloridate can be obtained from the reaction of sulfuryl chloride with two different thioates of the same configuration.



Scheme 8

Michalski [39a] has also found that the following two similar reactions lead to different optical isomers:



[37] *M. Green* and *R. F. Hudson*, Proc. chem. Soc. (London) *1962*, 217.

[38] *M. Green* and *R. F. Hudson*, Proc. chem. Soc. (London) *1959*, 227.

[39] *J. Michalski* and *R. Ratajczak*, Chem. and Ind. *1960*, 1241

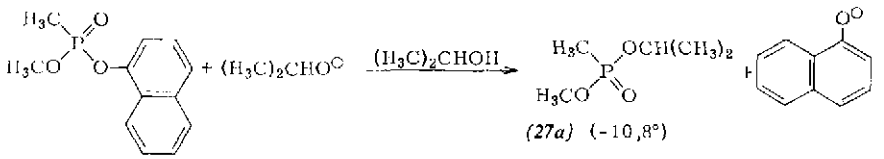
[39a] *J. Michalski*, personal communication.

b) Esters

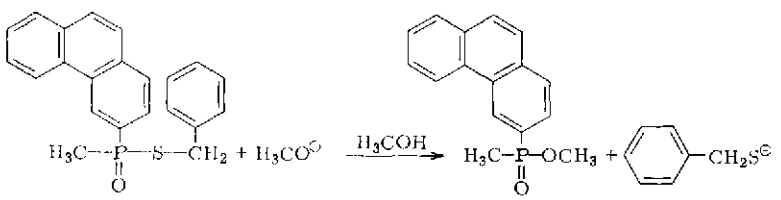
In view of the ease of racemization of optically active chloridates, other compounds such as esters, thioesters, and amides are more suitable for mechanistic investigations.

Preliminary measurements [40] showed that the 1-naphthoxy group and the *S*-benzyl group were rapidly removed by alkoxide ions from (+)-1-naphthylmethylmethylphosphonate *(27)* and (+)-*S*-benzyl 3-phenanthrylmethylphosphinothiolate *(28)* respectively, to give the optically active esters *(27a)* and *(29)*.

The changes in activity may be produced by overall inversion or retention of configuration, although the observed subsequent rapid racemization of *(29)* in the presence of an excess of methoxide ions suggests that the former is the case. Again, it can only be assumed that displacement of OR by OR′ and of SR by OR′ involve the same stereochemical change in a protolytic solvent [*].

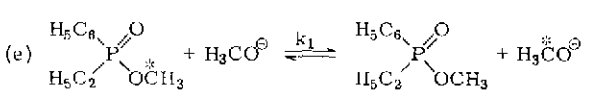


(27) (+44°) *(27a)* (−10,8°)

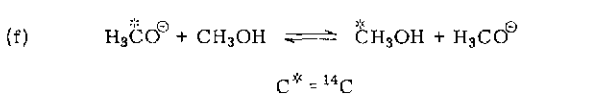


(28) (+17°) *(29)* (+61°)

Direct proof of the inversion mechanism has been obtained recently by comparing the rate of exchange of the methyl group, labelled with ^{14}C, of *O*-methyl ethylphenylphosphinate with methoxide ions, with the rate of racemization under the same conditions [41].



(e)

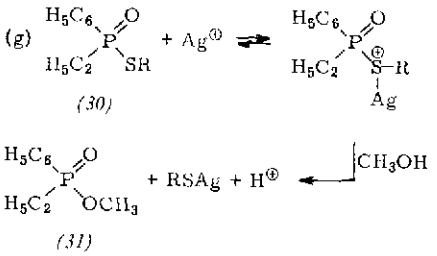


(f)

$C^* = {}^{14}C$

The subsequent equilibrium (f) ensures that the displacement (e) is effectively irreversible, hence the observed rate constant refers to the displacement (e). The pseudo-unimolecular rate constant for the racemization is twice k_1, showing that each act of substitution proceeds with inversion of configuration [**].

Since the stereochemical change may vary with the type of reaction, the following comparison was made. Kinetic investigations have shown that silver ions

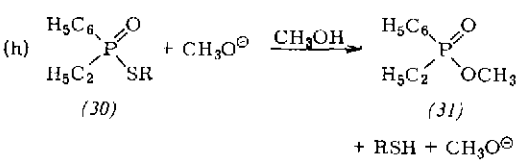


(g)

(30) *(31)*

strongly catalyse the hydrolysis of thiolates [42]. Similarly, the reaction with alcohol [43] is also catalysed by silver ions (g).

The optical activity of the *O*-ester *(31)*, which is produced in good yield, was of the same sign of rotation and very close to that obtained [4b] by displacement with methoxide ions (h).



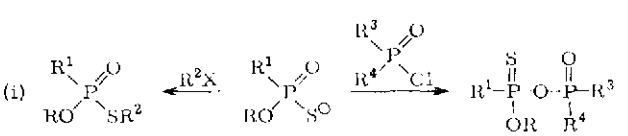
(h)

(30) *(31)*

This shows that both reactions proceed by the same stereochemical path, presumably with inversion of configuration. Attempts to react the thioester *(30)* with mercury alkyls in a search for a retention mechanism were unsuccessful [43].

c) Anhydrides

The preparative work of *Schrader* [44] has shown that thioic acids give *O*-pyrophosphates on phosphorylation, and this has been confirmed by N.M.R. measurements



(i)

[40] *M. Green*, Ph.D.thesis, London 1958.

[*] However, *Sommer* has shown [16] that displacement reactions at silicon atoms by hydroxide ions proceed by different stereochemical changes in water and xylene.

[41] *M. Green* and *R. F. Hudson*, Proc. chem. Soc. (London) *1962*, 307.

[**] This is the first *proof* of the nature of the stereochemical change accompanying substitution at a centre other than saturated carbon atoms.

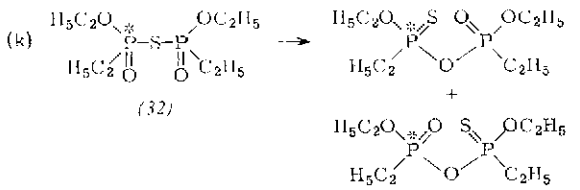
[42] *B. Saville*, J. chem. Soc. (London) *1961*, 4624.

[43] *M. Green* and *R. F. Hudson*, unpublished observations.

[44] *G. Schrader*, *W. Lorenz*, and *R. Mühlmann*, Angew. Chem. *70*, 690 (1958).

[45]. On the other hand, it is known that *S*-alkylation occurs exclusively in reactions at saturated carbon atoms.

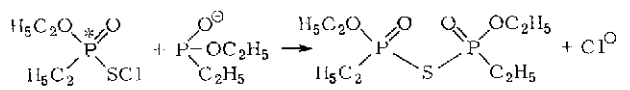
As pointed out by *Michalski* [46], however, the *O*-pyrophosphate may be formed by subsequent rearrangement of the *S*-pyrophosphate *(32)*. If this is so, the "disproportionation" (k) would occur when an optically active thioic acid is used.



(32)

Treatment of the isolated pyrophosphate with potassium methoxide would then give the original acid with only one half of the initial activity. In practice, however, the acid was found to have retained at least 90% of its initial activity, suggesting that the rearrangement (k) does not take place.

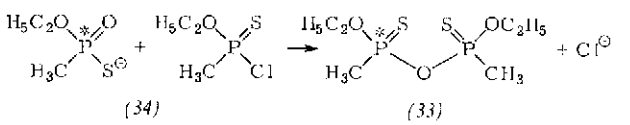
An alternative method involving nucleophilic attack by a phosphonite on the corresponding sulfenyl chloride was used in an attempt to prepare the isomeric pyrophosphate *(32)*.



(32)

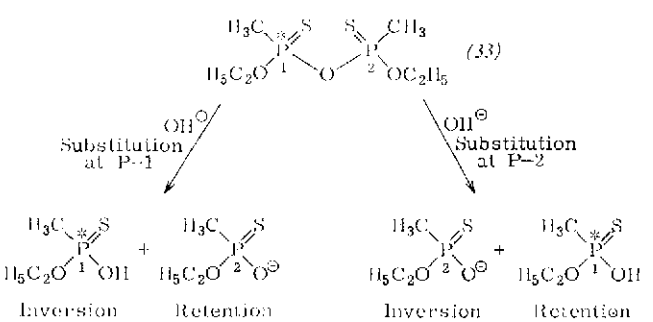
On treatment with potassium methoxide, the *O*-pyrophosphate isolated gave the thioic acid with *ca.* 50% retention of optical activity, supporting the rearrangement to the thermodynamically more stable isomer.

The thiopyrophosphate *(33)* with one asymmetric phosphorus atom has recently been prepared by the reaction of optically active *O*-ethyl methylphosphonothioic acid



(34) *(33)*

(34) and optically inactive *O*-ethyl methylphosphonochloridothionate [47].

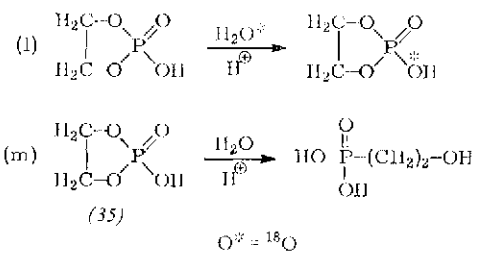


Scheme 9

Reaction of this optically active pyrophosphate with aqueous alkali gave the initial acid with almost zero activity. Since the displacement can occur with equal probability at either thiophosphoryl centre, the formation of racemic *O*-ethyl methylphosphonothioic acid demonstrates the absence of a retention mechanism, as illustrated in Scheme 9.

6. Cyclic Phosphates [*]

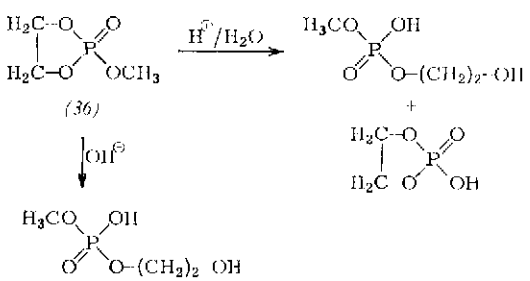
In addition to optical activity studies, investigations of molecules, particularly cyclic systems, in special conformations can provide additional stereochemical evidence. It is now well established that ethylenephosphate *(35)* is extremely reactive owing to the strain in the five-membered ring [48]. *Haake* and *Westheimer* [21] have recently shown that both ^{18}O exchange (l) and hydrolysis (m) proceed at similar rates in acid solution, but in alkaline solution, hydrolysis alone occurs.



(35)

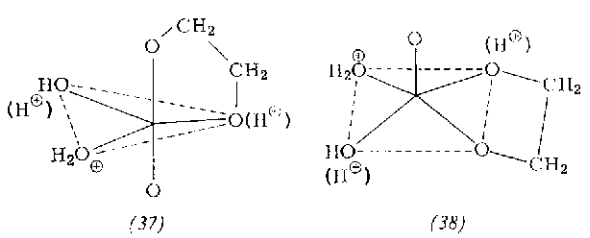
$O^* = {}^{18}O$

Similarly, alkaline hydrolysis of *O*-methyl ethylenephosphate *(36)* leads exclusively to ring opening, whereas acid hydrolysis gives a mixture of cyclic and open chain products [49].



(36)

The fact that the rates of hydrolysis of cyclic phosphates are *ca.* 10^7 times greater than the corresponding rates of the non-cyclic analogues, is due to the release from steric strain that occurs on formation of the transition state. Since reactions (l) and (m) are equally fast in acid



(37) *(38)*

[45a] *R. A. Y. Jones*, *A. R. Katritzky*, and *J. Michalski*, Proc. chem. Soc. (London) *1959*, 321.

[45b] *H. Finegold*, Ann. N. Y. Acad. Sci. *70*, 875 (1958).

[46] *J. Michalski*, *M. Mikolajczyk*, and *A. Ratajczak*, Chem. and Ind. *1962*, 819.

[47] *M. Green* and *R. F. Hudson*, J. chem. Soc. (London), in the press.

[*] For a recent review see *R. S. Emundson*, Chem. and Ind. *1962*, 1770.

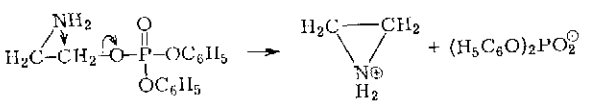
[48] *F. H. Westheimer*, Chem. Soc. Special Publication No. 8, London 1957, p. 1.

[49] *F. H. Westheimer*, personal communication.

solution, the O–P–O angle in the ring must be similar in the transition states of (l) and (m). If this angle is assumed [21] to be 90°, two structures are possible, *viz.* a trigonal bipyramid *(37)*, and a square pyramid *(38)*, respectively.

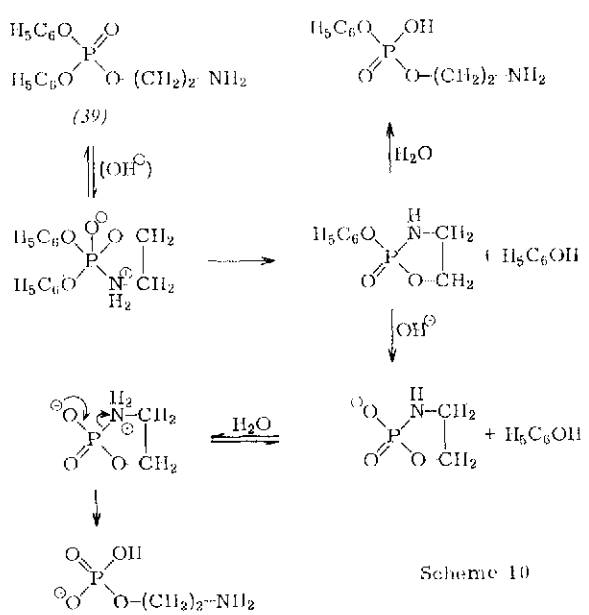
In the former structure, displacements would occur in the radial plane at a mutual angle of 120°. In the second structure, the four reacting bonds are equivalent, and reaction would lead to retention. No decision between these structures can be made at present, but these results show that alternative transition states are possible, and may be rationalized in terms of the general hypothesis advanced in Section 3: The transition state of the alkaline reaction – an anion with a high electron density on the phosphorus atom – will be of the S_N2 type with weak pd bonds along the reaction coordinate. The low electron density of the phosphorus atom of the protonated ester promotes the use of 3d-orbitals with the formation of a stabilized pentacovalent structure, thus allowing an alternative mode of decomposition.

The comparable rates of (l) and (m) show that the five-membered ring activates displacement of the exo-cyclic group, an unusual effect which could have synthetic uses. Thus (2-aminoethyl)diphenylphosphate *(39)* rapidly releases two moles of phenol in alkaline solution, although (2-aminoethyl)phenylhydrogen phosphate is unreactive in alkaline solution [50]. Moreover, in dilute alkaline solution, the reaction proceeds by the usual ionization reaction of nitrogen mustards giving ethylene imine and its cyclic dimer.



(39)

The first stage of the alternative reaction, being more dependent on OH^- concentration, may be base catalysed as are the reactions of amines with phenyl acetate [51].



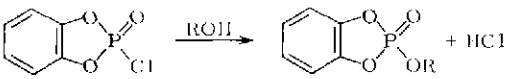
Scheme 10

[50] *G. J. Durrant, J. H. Turnbull,* and *W. Wilson,* Chem. and Ind. *1958*, 157.

[51] *W. P. Jencks* and *J. Carriuolo,* J. Amer. chem. Soc. *82*, 675 (1960).

These observations suggest the mechanism described in Scheme 10 involving an initial five-coordinated intermediate, and subsequent "cyclic activation" of the displacement of the second phenolic group [*].

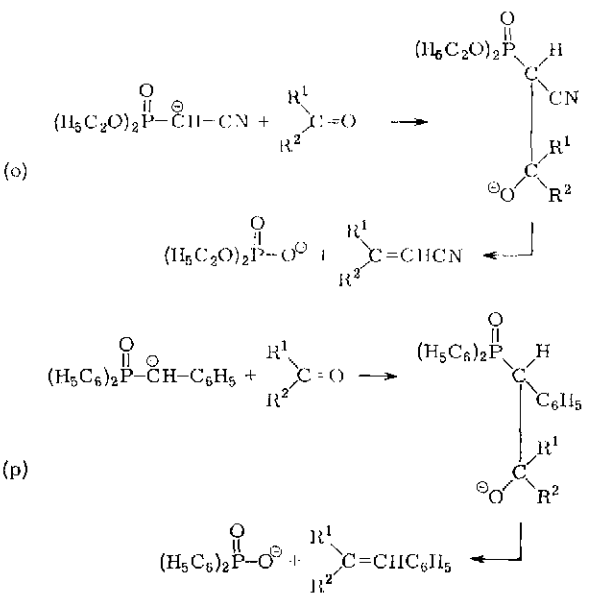
In a similar manner [52], derivatives of *o*-phenylene phosphate *(40)* are very reactive [53], and a similar type of activation may be in operation here. This possibility has however not been investigated kinetically.



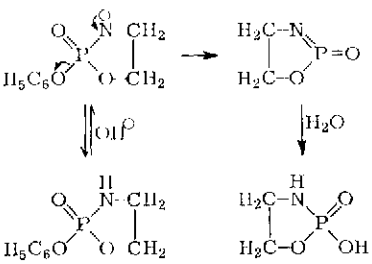
(40)

7. Rearrangement of Phosphonate Derivatives

Olefin syntheses analogous to the Wittig reaction have been established using phosphonates and phosphine oxides [54]. These methods involve elimination from intermediates formed by the reaction of the stabilized carbanions with ketones and aldehydes.



[*] Alternatively, this stage may proceed through the intermediate ion in a unimolecular decomposition [52]:



[52a] *F. H. Westheimer,* [48], p. 180.

[52b] *E. W. Crunden* and *R. F. Hudson,* Chem. and Ind. *1958*, 1478.

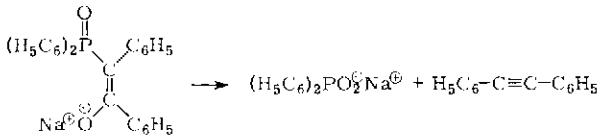
[53] *W. S. Reich,* Nature (London) *157*, 133 (1946).

[54a] *L. Horner, H. Hoffmann,* and *H. G. Wippel,* Chem. Ber. *91*, 61 (1958).

[54b] *L. Horner, H. Hoffmann, H. G. Wippel,* and *G. Klahre,* Chem. Ber. *92*, 2499 (1959).

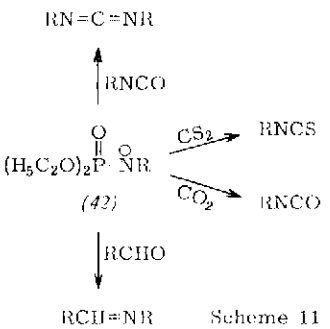
[54c] *W. S. Wadsworth* and *W. D. Emmons,* J. Amer. chem. Soc. *83*, 1733 (1961).

Recently [34], an analogous acetylene synthesis has been described, in which pyrolysis of the phosphine oxide *(41)* results in elimination of the sodium salt of diphenylphosphinic acid.



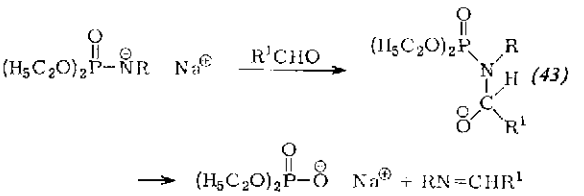
(41)

The anions of dialkylphosphoramidates *(42)* have been shown [55] to react with carbonyl compounds in a similar manner to iminophosphines [33] and phosphorimidates [56].

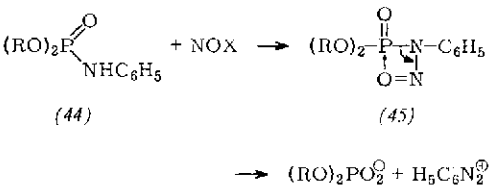


Scheme 11

As in the phosphonate olefin synthesis, the reactions probably involve eliminations of the sodium salt of diethylphosphonic acid from the intermediate *(43)*.



The formation [57] of diazonium phosphates by nitrosation of *N*-arylphosphoramidates *(44)* probably also occurs through a four-membered cyclic intermediate *(45)* as follows:



The facility with which all these reactions occur strongly suggests that four-centred intermediates are readily formed at a phosphoryl centre, although the molecularity of these reactions has not been established. Such a configuration is readily understood if d-orbital hybridisation is assumed (see structure *(10)*, Section 3), although, as indicated in Section 2, it is not essential to invoke high energy levels to explain alternative structures. Investigations of these reactions with optically active phosphoryl compounds would be of great interest.

Received, August 27th, 1962 [A 260/61 IE]

[55] *W. S. Wadsworth* and *W. D. Emmons*, J. Amer. chem. Soc. *84*, 1316 (1962).

[56] *M. I. Kabachnik* and *V. A. Gilyarov*, Izvest. Akad. Nauk. S.S.S.R., Otdel. Khim. Nauk *1956*, 790.

[57] *P. J. Bunyon* and *J. I. G. Cadogan*, J. chem. Soc. (London) *1962*, 1304.

Reactive Dyes Containing Vinylsulfonyl Groups

BY DR. J. HEYNA

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Compounds and dyes containing vinylsulfonyl groups or groupings which readily yield vinylsulfonyl groups possess a marked ability to add onto many compounds containing active hydrogen under alkaline conditions. They also react with natural substances of high molecular weight, e.g. wool and cellulose, which contain amino- or hydroxyl groups. These reactions lead to the formation of strong covalent bonds between the reactants. As a result of this finding, reactive dyes for nitrogenous and cellulose fibers have been developed.

1. Introduction

In recent years, reactive dyes have achieved considerable scientific and commercial importance. This is because their use for dyeing natural and synthetic fibers results in strong chemical bonds between fiber and dye. This new development in the dyestuffs field has recently been reviewed by *Zollinger* [1]. The following is a description of the work done at Hoechst on reactive dyes containing vinylsulfonyl groups.

Research at Farbwerke Hoechst on compounds and dyes containing vinylsulfonyl groups or groupings which readily yield

[1] *H. Zollinger*, Angew. Chem. *73*, 125 (1961).

vinylsulfonyl groups started towards the end of 1948. It was found that dyes containing such groups (hereinafter referred to as vinyl sulfone dyes) give wool dyeings with high fastness to wet processing. In 1949, it was realized that these good fastness properties arise from a chemical bond between the dye and the fiber. Further work disclosed the suitability of these dyes for dyeing cellulose fibers and showed that they form strong chemical bonds with cotton. Based on these findings, several assortments of reactive dyes for wool and cotton were developed.

Knowledge of the reactions of simple compounds containing vinylsulfonyl groups or groupings that readily yield vinylsulfonyl groups is useful for a thorough understanding of the properties of vinyl sulfone dyes. Hence, before considering the dyes, let us examine the corresponding simple compounds, particularly those containing β-sulfato-ethylsulfonyl groups.

2. Chemical Behavior of Sulfates of β-Hydroxyethyl Sulfones

Variously substituted, particularly aromatic, compounds, containing β-sulfato-ethylsulfonyl groups can be prepared readily by esterification of β-hydroxyethyl sulfones with sulfuric acid (Reaction 1). On neutralization with alkali, they are converted into water-soluble, stable alkali salts. Further addition of alkali results in most cases in nearly quantitative formation of vinylsulfonyl compounds (Reaction 2) [2]. This reaction is very fast even at room temperature. Vinyl sulfone formation can perhaps be explained by assuming that the weakly basic sulfate ion is formed particularly easily once a proton is eliminated from the α-methylene group. Compounds containing the β-sulfato-ethylsulfonyl group may therefore be considered to be masked vinyl sulfones.

$$R{-}SO_2{-}(CH_2)_2{-}OH \xrightarrow{+\ H_2SO_4} R{-}SO_2{-}(CH_2)_2{-}OSO_3H \quad (1)$$

$$R{-}SO_2{-}(CH_2)_2{-}OSO_3^{\ominus} \xrightarrow{+\ OH^{\ominus}} R{-}SO_2{-}\overset{\ominus}{C}H{-}CH_2{-}OSO_3^{\ominus} \quad (2)$$

$$\longrightarrow R{-}SO_2{-}CH{=}CH_2$$

At higher temperatures, under the catalytic influence of alkali, the resulting vinyl sulfones add on water more or less readily to yield β-hydroxyethyl sulfones (Reaction 3), which can react further with excess vinyl sulfone to give ethers (Reaction 4). On treatment with hot strong alkalis, some of these ethers undergo cleavage to reform β-hydroxyethyl sulfones (Reaction 5).

$$R{-}SO_2{-}CH{=}CH_2 + H_2O \xrightarrow[\text{heat}]{OH^{\ominus}} R{-}SO_2{-}(CH_2)_2{-}OH \quad (3)$$

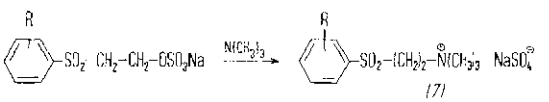
$$R{-}SO_2{-}(CH_2)_2{-}OH + R{-}SO_2{-}CH{=}CH_2 \rightarrow \begin{matrix} R{-}SO_2{-}(CH_2)_2 \\ \diagdown \\ \qquad O \\ \diagup \\ R{-}SO_2{-}(CH_2)_2 \end{matrix} \quad (4)$$

$$\begin{matrix} R{-}SO_2{-}(CH_2)_2 \\ \diagdown \\ \qquad O \\ \diagup \\ R{-}SO_2{-}(CH_2)_2 \end{matrix} + H_2O \xrightarrow[\text{heat}]{OH^{\ominus}} 2\ R{-}SO_2{-}(CH_2)_2{-}OH \quad (5)$$

Strong, hot acids such as hydrochloric or sulfuric acid hydrolyze the β-sulfato-ethylsulfonyl compounds to give β-hydroxyethyl sulfones. Weak acids such as acetic acid do not attack the ester group even on prolonged boiling. β-Sulfato-ethylsulfonyl compounds react readily with compounds containing labile protons, especially in an alkaline medium. Thus, with ammonia or primary or secondary amines, β-aminoethyl sulfones are formed particularly easily [3]. In this reaction, several hydrogen atoms of the amine may be substituted by sulfonylethyl residues (Reaction 6).

$$2\ R{-}SO_2{-}(CH_2)_2{-}OSO_3Na \xrightarrow[NaOH]{+\ CH_3{-}NH_2} \begin{matrix} R{-}SO_2{-}(CH_2)_2 \\ \diagdown \\ \qquad N{-}CH_3 \\ \diagup \\ R{-}SO_2{-}(CH_2)_2 \end{matrix} \quad (6)$$

The reaction of tertiary amines with β-sulfato-ethylsulfonyl affords quaternary ammonium compounds (Reaction 7) [4]. Aqueous alkalis readily convert these compounds into vinyl sulfones [5].



(7)

In the presence of alkali, salts of β-sulfato-ethylsulfonyl react with alcohols, phenols, and naphthols, both in the undiluted state and in aqueous solution, to give ethers (Reaction 8). Polyhydroxy compounds such as ethylene glycol, glycerol or poly(vinyl alcohol) undergo a multiple reaction. With compounds containing two β-sulfato-ethylsulfonyl groups, cross-linking can occur. Thus, poly(vinyl alcohol) may be converted into water-insoluble fibers or films [6]. To ensure that all these reactions proceed smoothly, it is essential to use only a very small amount of alkali, otherwise the β-sulfonyl ether will be cleaved by the strong alkali, especially at high temperatures.

$$R{-}SO_2{-}(CH_2)_2{-}OSO_3Na \xrightarrow[NaOH]{HOR'} R{-}SO_2{-}(CH_2)_2{-}OR' \quad (8)$$

Vinyl sulfones and sulfate esters of β-hydroxyethyl sulfones react readily with proteins. For example, polyfunctional vinyl sulfones are good hardening agents for photographic gelatin coatings [7].

When woolen felt is treated, for example, with the sodium salt of 3,4-dichlorophenyl β-sulfato-ethyl sulfone in a neutral bath at boiling temperature, quantitative absorption of this compound by the wool takes place. The fixation on wool is fast to washing, as indicated by the fact that the chlorine content of the wool fibers remains unaltered on washing [8]. It has not yet been clearly established which groups of the wool protein react with the vinylsulfonyl group.

[2] German Patent 842198 (Jan. 8th, 1942); I.G. Farbenindustrie; inventors: *G. Kränzlein, J. Heyna,* and *W. Schumacher.*

[3] German Patent 635298 (June 16th, 1934); I. G. Farbenindustrie; inventor: *H. Ufer.*

[4] German Patent 1064055 (Sept. 10th, 1952); Farbwerke Hoechst AG.; inventors: *J. Heyna* and *W. Riemenschneider.*

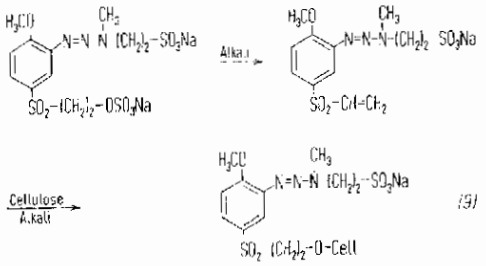
[5] German Patent 932488 (Sept 11th, 1952); Farbwerke Hoechst AG.; inventors: *J. Heyna* and *W. Riemenschneider.*

[6] German Patent 1080261 (June 21st, 1952); Farbwerke Hoechst AG.; inventors: *J. Heyna, W. Starck,* and *H. Starck.*

[7] German Patent 872153 (May 6th, 1944); Farbenfabriken Bayer; inventors: *W. Kleist, O. Bayer,* and *J. Heyna.* German Patent 1100942 (March 19th, 1958); Farbwerke Hoechst AG.; inventors: *J. Heyna, L. Berlin,* and *E. Schinzel.*

[8] German Patent 965902 (July 19th, 1949); Farbwerke Hoechst AG.; inventors: *J. Heyna* and *W. Schumacher.*

Fixation on cotton of diazoamino compounds containing a β-sulfato-ethylsulfonyl group occurs at 80–85 °C from a weak sodium alkali bath, in the presence of sodium sulfate (Reaction 9). The diazoamino compound attached to the fiber can be cleaved to give a diazo compound when, after thorough rinsing, a small amount of mineral acid is added to the last rinsing solution. Azo dyes may then be produced on the fiber with various coupling agents. The fastness of these dyes to wet processing is good to very good [8].



(9)

By analogy to "cyanoethylation", this procedure may be named "sulfoethylation" of cellulose. The ether bond formed in the reaction is unusually stable in neutral and acidic media. In boiling strong alkali, however, because of the sulfonyl group in the β-position, this bond undergoes cleavage more or less readily (cf. Reaction 5).

3. Dyeing Behavior of Vinyl Sulfone Dyes

With respect to their reactive properties, vinyl sulfone dyes are very similar to the colorless vinyl sulfones and β-sulfato-ethylsulfonyl compounds. The dyeing behavior of vinyl sulfone dyes which do not also contain any sulfo or carboxy groups in addition to the β-sulfato-ethylsulfonyl group is different from that of vinyl sulfone dyes containing additional groups to make them soluble in water. The two types will therefore be treated separately.

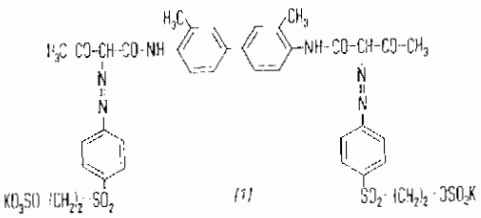
a) Vinyl Sulfone Dyes without Additional Substituents Imparting Solubility in Water

Dyes of this type may be used for dyeing cellulose ester fibers. Their β-sulfato-ethylsulfonyl group is split off by the action of hot, weak alkalis, *e.g.* soap solution. The resulting vinyl sulfone dyes precipitate in an unusually fine and uniformly dispersed form and are absorbed from this dispersion by the fiber. In place of soap and weak alkalis, compounds may be used which undergo decomposition in hot, aqueous solution to give alkaline cleavage products. Cellulose ester fibers as well as other synthetic fibers such as polyamides and polyesters can be dyed satisfactorily with these dyes, with good penetration [8,9].

In general, the dyeings possess very good fastness to wet processing and good or very good fastness to light. As a result, certain representatives of this dye class have achieved practical significance.

[9] German Patent 946975 (June 10th, 1952); Farbwerke Hoechst AG.; inventors: *J. Heyna, A. Carl,* and *H. D. Wagner.*

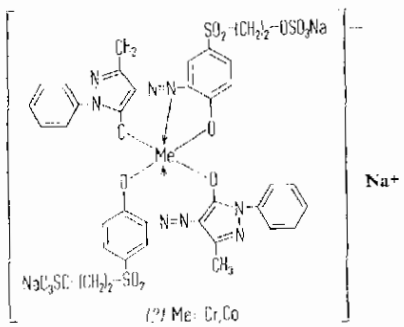
These dyes may also be applied to wool and cellulose fibers. The dye of formula *(1)*, for example, may be used to dye or print wool and cotton by special processes; it produces yellow dyeings with very good fastness to wet processing.



(1)

2,2′-Dihydroxyphenyl-azo dyes with vinylsulfonyl or β-sulfato-ethylsulfonyl groups possess valuable properties as chrome dyes and metal complex azo dyes. They have found practical application as metachrome and afterchrome dyes. Examples are Metachrome Orange H3R, Metachrome Gray RL, Salicinchrome Orange H3R, and Salicinchrome Gray RL.

Metalation of 2,2′-dihydroxyphenyl-azo and 2-hydroxy-2′-aminophenyl-azo dyes containing alkali salts of β-sulfato-ethylsulfonyl groups with chromium or cobalt salts yields 1:2 metal complex dyes if a proportion of one metal atom to two molecules of azo dye is used [10]. The type of structure assumed for these dyes is illustrated, for example, by formula *(2)*; they are most probably analogous to other 1:2 metal complex azo dyes already known. In many cases, acids will not precipitate these dyes from their aqueous solutions, in contrast to the reaction with dyes which contain alkylsulfonyl groups in place of β-sulfato-ethylsulfonyl groups. With alkali, they can be converted into dyes containing one or two vinylsulfonyl groups.



(2) Me: Cr, Co

These 1:2 metal complex dyes possess a marked dyeing affinity, particularly at mildly acidic pH values; they are suitable for dyeing wool, polyamide fibers, and leather. Their dyeings are characterized by good or very good fastness to wear and processing. Because of these properties, a series of chrome and cobalt complex dyes based on dyes containing vinylsulfonyl groups was commercially introduced in 1958 (Remalan® Fast Dyes). Some of these metal complex dyes were also marketed as Coranil® Fast Dyes for leather.

[10] German Patent 940482 (March 12th, 1953); Farbwerke Hoechst AG.; inventors *J. Heyna, O. Hensel,* and *W. Schumacher.* German Patent 953103 (July 17th, 1954); Farbwerke Hoechst AG.; inventor: *J. Heyna.* German Patent 1012010 (May 14th, 1955); Farbwerke Hoechst AG.; inventors *J. Heyna, W. Schumacher,* and *G. Jacobsen.*

Dyeing and printing of cellulose fibers can also be accomplished with 1:2 chrome and cobalt complex azo dyes containing β-sulfato-ethylsulfonyl groups. A process for fixing these dyes on cotton consists, for example, of applying the water-soluble dyes to the fiber, and subjecting the goods thus treated to the action of poly-(alkylene-imines) and alkalies, such as alkali hydroxides, carbonates, or phosphates [11]. This process yields dyings on cotton that are fast to washing. In contrast, dyes which contain methyl-, ethyl-, or β-hydroxyethylsulfonyl groups in place of the β-sulfato-ethylsulfonyl groups do not undergo fixation.

b) Vinyl Sulfone Dyes with Additional Substitutents Imparting Solubility in Water

Numerous vinyl sulfone dyes containing additional sulfonic or carboxylic acid groups have been prepared and evaluated for their suitability in dyeing nitrogenous fibers and cotton [12]. It was found that good dyeings with very good fastness to wet processing can be achieved on both types of fibers and that the dye is attached to the fiber by covalent chemical bonds. Dyes containing sulfonic and carboxylic acid groups and belonging to the most diverse classes, such as azo, anthraquinone, phthalocyanine, nitro, and triphenylmethane dyes, may be used. From the standpoint of fastness to wet processing, it is unimportant whether the reactive group in these dyes is a vinylsulfonyl group or a group which readily yields a vinylsulfonyl group under the dyeing conditions.

Dyeing of wool with vinyl sulfone dyes containing sulfonic or carboxylic acid groups is carried out in a neutral or slightly acidic bath, in order to achieve high fastness to wet processing. Under these conditions, the acid groups of the dyes probably first form salts with the functional groups, for example, with the amino groups of wool keratin. The reaction between the dyes and the fiber is completed by an alkaline after-treatment [13]. Polyamide fibers can be dyed similarly with vinyl sulfone-type dyes to give dyeings fast to wet processing.

At the end of 1952 and early in 1953, two vinyl sulfone dyes for wool and polyamide fibers, *viz.* Remalan® Brilliant Blue B and Remalan ®Yellow GG, were introduced commerically. They were the first reactive dyes for wool to appear on the market [14].

In the presence of alkali, vinyl sulfones and sulfates of β-hydroxyethyl sulfones react with the hydroxyl groups of cotton. The application of this reaction to vinyl sulfone dyes containing additional sulfonic or carboxylic acid groups has led to new dyestuffs which have achieved commercial significance as reactive dyes for cellulose fibers under the name of Remazol® dyes. Ample proof for the establishment of a covalent chemical bond between Remazol dyes and the cotton fiber has been obtained during recent years [15]. Ether formation between the dye and cellulose, similar to reaction (9), takes place (Reaction 10).

$$F{-}SO_2{-}CH{=}CH_2 \xrightarrow[\text{alkali}]{\text{cellulose}} F{-}SO_2{-}(CH_2)_2{-}O{-}\text{cellulose} \quad (10)$$

F = dye radical

Thus, the bond formed by Remazol dyes differs from that of the Procion® and Cibacron® dyes, which are attached to cellulose by ester linkages.

What has been said about the stability of simple β-sulfonyl ethers is also true with regard to the strength of the dye-fiber bond. Accordingly, the bond is relatively stable in neutral, acidic, or slightly alkaline medium, whereas under the action of stronger alkali, particularly at elevated temperature, partial cleavage of the ether bond may take place.

It is surprising that vinyl sulfone dyes react at all with the hydroxyl groups of cellulose in an aqueous alkaline dye bath and not exclusively with water. During the dyeing process, a portion of the dye, however, always reacts with water. By analogy to the reactions of simple vinyl sulfones or β-sulfato-ethylsulfonyl compounds, this reaction probably yields dyes containing β-hydroxyethylsulfonyl groups or ether-type derivatives thereof. In dyeing practice, it is important that these non-fixed dye particles be removed from the fiber, otherwise the fastness of the dyeing to wet processing will be unfavorably affected.

Non-substantive or only slightly substantive, water-soluble vinyl sulfone dyes are suitable for use as Remazol dyes. Dyes of practical significance are primarily azo, metal complex azo, anthraquinone, and phthalocyanine dyes. The first six Remazol dyes appeared on the market in 1957. Many different processes for applying Remazol dyes have been described in numerous publications [16].

Dyeings with Remazol dyes possess remarkable fastness. In this respect, they occupy a place between after-treated direct dyes and Indanthrene® dyes. Additional properties of this dye class are good dischargeability, good performance on treatment with synthetic resins, and resistance to acidic industrial gases. Most Remazol dyeings possess good or excellent fastness to light.

The author wishes to thank all those who have participated in this work; particularly he remembers his late colleague and coworker, Dr. Willy Schumacher.

Received, July 5th, 1962 [A 245/63 IE]

[11] German Patent 1062667 (Sept. 7th, 1956); Farbwerke Hoechst AG.; inventors: *J. Heyna, W. Schumacher,* and *W. Noll.*

[12] German Patent 960534 (Jan. 10th, 1950); Farbwerke Hoechst AG.; inventors: *J. Heyna* and *W. Schumacher.* German Patent 966651 (July 4th, 1950); Farbwerke Hoechst AG.; inventors: *J. Heyna* and *W. Schumacher.* German Patent 925121 (February 20th, 1952); Farbwerke Hoechst AG.; inventors: *J. Heyna, O. Hensel,* and *W. Schnorrenberg.*

[13] *F. Osterloh,* Melliand Textilber. *41,* 1533 (1960).

[14] *F. Schlaeppi,* Amer. Dyestuff Reporter *47,* 377 (1958); *H. Zollinger:* Chemie der Azofarbstoffe [Chemistry of Azo Dyes]. Birkhäuser, Basel 1958, pp. 181 and 183.

[15] *E. Bohnert,* Melliand Textilber. *42,* 1156 (1961).

[16] *O. Ziegler,* Melliand Textilber. *39,* 66 (1958); *H. Zimmermann,* ibid. *39,* 1026 (1958); *E. Bohnert* and *R. Weingarten,* ibid. *40,* 1036 (1959); *H. U. von der Eltz* and *F. Osterloh,* ibid. *40,* 1445 (1959); *H. U. von der Eltz,* ibid. *40,* 69 (1959); *A. Bode,* ibid. *40,* 1304 (1959); *H. Zimmermann,* ibid. *41,* 1555 (1960); *E. Ungermann,* ibid. *42,* 89 (1961); *H. U. von der Eltz,* ibid. *42,* 671, 929 (1961); *E. P. Sommer,* Amer. Dyestuff Reporter *47,* 895 (1958); *E. Ungermann* and *W. Hacker,* SVF-Fachorgan *15,* 111 (1960); *H. U. von der Eltz* and *H. Wachner,* ibid. *16,* 325 (1961).

Syntheses in the 3-Aminoquinazol-4-one and 3-Aminobenzotriazin-4-one Series

BY DR. S. PETERSEN, DR. H. HERLINGER, DR. E. TIETZE, AND DR. W. SIEFKEN

WISSENSCHAFTLICHES HAUPTLABORATORIUM DER FARBENFABRIKEN BAYER AG., LEVERKUSEN (GERMANY)

Dedicated to Professor Dr. Otto Bayer on the occasion of his 60th birthday

Among the derivatives of 3-aminoquinazol-4-one and 3-aminobenzotriazin-4-one are compounds with narcotic, sedative, analgetic, and muscle-relaxant properties. Of special interest are compounds with one or several urethane groups and those substituted in the 3-position by a morpholine moiety.

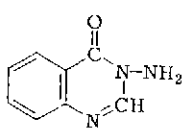
Introduction

Many pharmacologically or chemotherapeutically active compounds may be considered as derivatives of hydrazine. They contain an –N–N– group either in a heterocyclic ring (pyrazolones, antipyrine, pyramidone, butazolidine, sulfapyridazine, sulfathiadiazole, hydrazino- and dihydrazinophthalazine, cyclopentamethylenetetrazole) or in the side chain (isonicotinic hydrazide, thiosemicarbazones of aldehydes, quinone guanylhydrazone thiosemicarbazone) [1].

In the synthesis of pharmaceuticals, less attention has been paid to hydrazine derivatives in which only one nitrogen atom is heterocyclic,while the other one belongs to the *N*-amino group in the side chain [2].

The side chain can, of course, be heterocyclic on its own account, as is the case with compounds of the type:

Among the many compounds with this general structure, we were especially interested in derivatives of 3-aminoquinazol-4-one *(1)* and 3-aminobenzotriazin-4-one *(2)*, *i.e.* compounds which contain both structural elements of an *o*-aminoarylcarboxylic acid (anthranilic acid) and of a hydrazine participating with a nitrogen atom in a hetero ring. Several of the compounds investigated show useful pharmacological properties.



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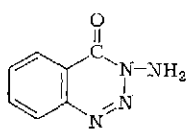


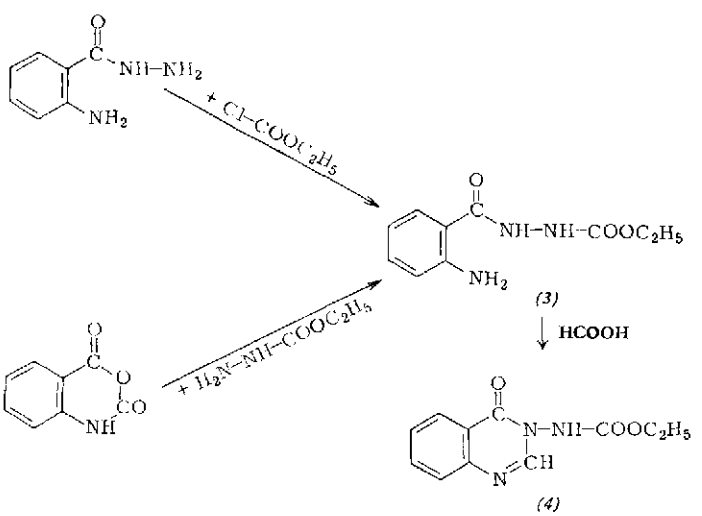
(2)

[1] *E. Jucker*, Angew. Chem. *71*, 321 (1959), Table 1.

[2] This type includes the derivatives of 1-aminoacetidinedione described by *E. Jucker:* Angew. Chem. *71*, 331 (1959); *A. H. Beckett* and *J. V. Greenhill*, J. med. pharm. Chem. *4*, 423 (1961).

3-Aminoquinazolones

Acylated 3-aminoquinazolones have already been synthetized by *Heller* [3].



Another hitherto undescribed method for the preparation of *(3)* applies the reaction of isatoic anhydride with ethoxycarbonylhydrazine. This reaction proceeds particularly elegantly and gives high yields. As will be shown in the following, this reaction can be used with many other monoacylated hydrazines.

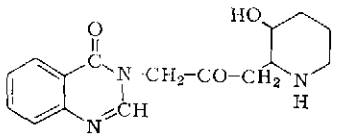
Even the simple, well known 3-(ethoxycarbonylamino)-quinazol-4-one *(4)* was shown to possess sedative properties during tests conducted in our laboratories in Elberfeld (*M. Bock*; see Table 2, a).

Quinazolones with pharmacological activity have been known for some time. The elucidation of the structure of the antimalarial alkaloid febrifugine [4], stimulated the investigation of the quinazolone system in various laboratories. Thus, during the exploration of improved antimalarial agents, a

[3] *G. Heller*, J. prakt. Chem. (2) *116*, 1 (1927).

[4] *J. A. Brockman* and *J. Moffat*, J. Amer. chem. Soc. *72*, 3323 (1950); *B. R. Baker*, J. org. Chemistry *17*, 35 (1952); *O. Ju. Magidson* and *Zu Jui-Chua*, J. prakt. Chem. (russ.) *29*, 2843, 3299 (1959).

hypnotic [5] was found which was marketed under the names Melsedin® and Revonal®. These investigations became known to us only during the course of our own work.



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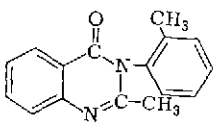


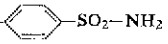
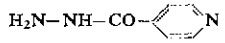
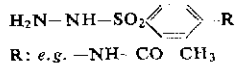
Revonal®

The first pharmacological findings with 3-(ethoxycarbonylamino)quinazol-4-one prompted us to systematically investigate the 3-aminoquinazolones.

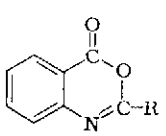
Substituents in the 3-position of the quinazolone ring can be modified quite simply via the reaction of various hydrazines or hydrazides with isatoic anhydride to form *o*-aminoarylcarboxylichydrazides, followed by ring closure to give quinazolone. Several of the hydrazine derivatives which we have used are shown in Table 1.

The quinazolone ring was closed using formic acid or its equivalents (*e.g.* formamide). Direct ring closure with higher fatty acids proceeds in poor yield or not at all. Thus, introduction of substituents at C-2 is conveniently accomplished with "acylanthranilic anhydrides", *i.e.* 6-oxo-4,5-benz-1,3-oxazines which are substituted at C-2, by reaction with the hydrazine derivatives shown in Table 1.

Table 1. Hydrazines and hydrazides used in the synthesis of quinazolones

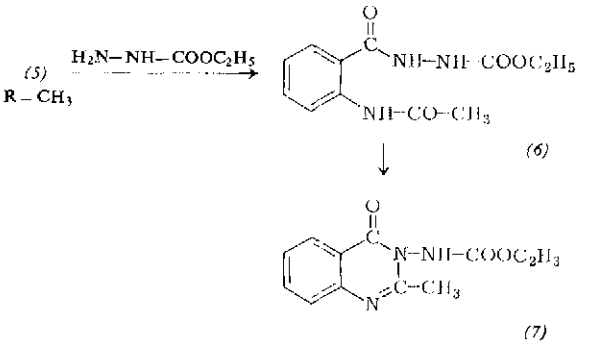
Hydrazide	Hydrazine
$H_2N-NH-CO-OR$ (ROH: various alcohols)	H_2N-NH_2
$H_2N-NH-CO-CH_3$	$H_2N-NH-CH_2-CH_2-CN$
$H_2N-NH-CO-CH_3$	
$H_2N-NH-CO-C_{11}H_{23}$	
$H_2N-HN-CO-CH_2-CN$	
	
$H_2N-NH-SO_2-CH_3$	
	
R: *e.g.* $-NH-CO-CH_3$	

Anthranilic acid and acetic anhydride, for example, give the simple acetylanthranilic anhydride *(5)*, where R = CH_3. This can be split with ethoxycarbonylhydrazine to give 2-acetamino-N^2-ethoxycarbonylbenzhydrazide *(6)*. On prolonged heating the two components, or by reacting them in glacial acetic acid, 2-methyl-3-ethoxycarbonylaminoquinazol-4-one *(7)* is formed directly (see Table 2, b).



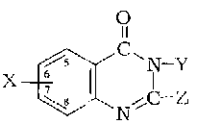
(5)

R: *e.g.* CH_3, $-C_2H_5$, $-CH(CH_3)_2$, $-CH_2-O-CH_3$, $-COOC_2H_5$



This procedure is applicable to all the hydrazine derivatives mentioned in Table 1. It is noteworthy that this reaction sequence for hydrazines can also be applied to acylhydrazines.

Table 2. 3-Aminoquinazolones

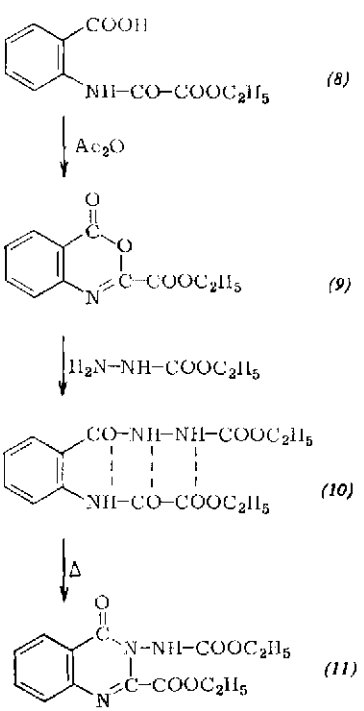


	X	Z	M.p. [°C]	Activity
		$Y = -NH-COOC_2H_5$		
a		$-H$	181–182	tranquilizing
b		$-CH_3$	127–128	narcotic, induces muscle spasms
c		$-C_2H_5$	114–117	narcotic, induces muscle spasms, weakly analgetic
d		$-COOC_2H_5$	108	narcotic
e	$-CH_3$ *(7)*	$-H$	207	narcotic, induces muscle spasms
f	$-Cl$ *(5)*	$-CH_3$	151–153	narcotic, induces muscle spasms
g	$-COOC_2H_5$ *(7)*	$-CH_3$	117	briefly narcotic
h	$-SO_2N(CH_3)_2$ *(6)*	$-H$	190–191	inactive
		$Y = -NH-COO-CH_2-CH=CH_2$		
i		$-H$	133–134	prolonged narcotic, induces muscle spasms
		$Y = -NH-CO-CH_2-CN$		
k		$-H$	227–230	inactive
		$Y = -NH-CO-$		
l		$-H$	202–204	weakly hypnotic
		$Y = -NH-SO_2-$		
m	$-Cl$ *(6)*	$-CH_3$	228 (acetyl deriv. 259)	no sulfonamide action
		$Y =$		
n		$-CH_3$	300–303 (hydrochloride)	analgetic
o		$-COOC_2H_5$	121–122	analgetic and hypnotic

An interesting starting material for our synthesis was an "acylanthranilic anhydride" of the formula *(5)*, where R signifies an ethoxycarbonyl group *(9)*. It was obtained by heating ethyl (2-carboxyphenyl)oxamate *(8)* with acetic an-

[5] *J. Kacker* and *S. H. Zaheer*, J. ind. chem. Soc. *28*, 344 (1951); American Cyanamid US.-Patent 2621162, 2625549, 2648665, 2651632, 2651633, 2694711, 2796417, 2811524, inventor: *B. R. Baker*.

hydride [6]. In this case, the reaction of *(9)* with ethoxycarbonylhydrazine stops at the open chain compound *(10)*. The latter absorbs strongly in the ultraviolet and shows a sharp drop of extinction toward the region of visible light (*M. Pestemer*). It is possible that hydrogen bonds are formed between the side chains and that they are responsible for this effect. Only upon melting *in vacuo* does *(10)* lose one mole of water, whereupon it forms the desired quinazolone *(11)* (see Table 2, d).

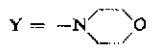


We synthetized numerous quinazolones with further substituents in the benzene ring. It is best to introduce these substituents at the anthranilic acid or isatoic anhydride level (see Table 2, e–h, m).

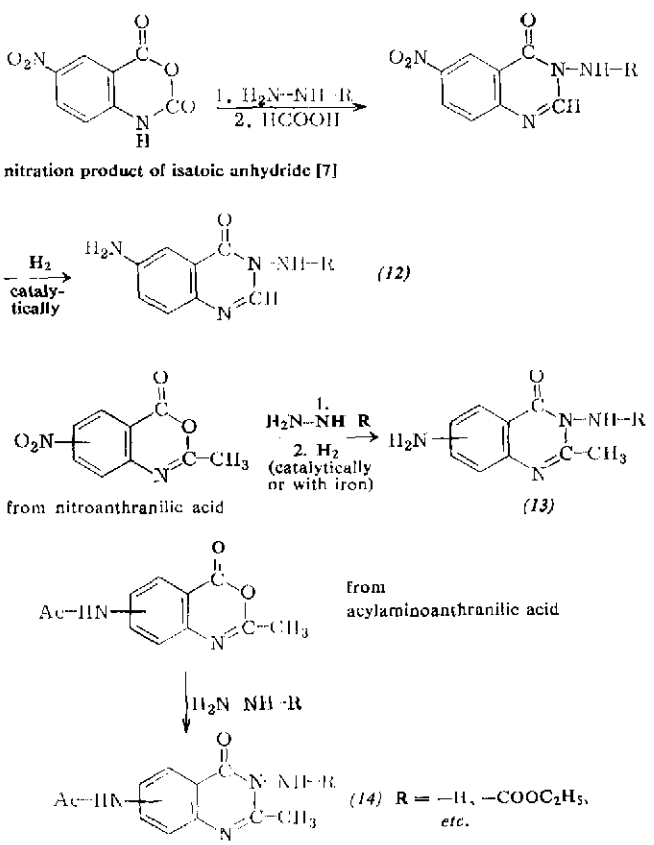
[6] *M. T. Bogert* and *R. A. Gortner*, J. Amer. chem. Soc. *32*, 119 (1910).

Significant activity was exhibited by 3-aminoquinazolones bearing an additional amino group at the benzene nucleus, *e.g. (12)–(14)* [7,8]; see Table 3.

Table 3. Diaminoquinazolones (for formula see Table 2)

	X	Z	M.p. [°C]	Activity
		Y = $-NH_2$		
a	$-NH_2$ *(6)*	$-CH_3$	232	inactive
b	$-NH-COOC_2H_5$ *(6)*	$-CH_3$	234	muscle relaxant
		Y = $-NH-COOC_2H_5$		
c	$-NH_2$ *(6)*	$-H$	200–202	weakly narcotic, muscle relaxant
d	$-NH-COOC_2H_5$ *(5)*	$-CH_3$	169–170	
e	$-NH-COOC_2H_5$ *(6)*	$-CH_3$	193–195	hypnotic, muscle relaxant
f	$-NH-COOC_2H_5$ *(7)*	$-CH_3$	195–196	weakly hypnotic, muscle relaxant
g	$-NH-COOC_2H_5$ *(8)*	$-CH_3$	170–171	hypnotic, muscle relaxant
h	$-NH-COCH_3$ *(6)*	$-CH_3$	191–193	inactive
		Y = $-NHCOOCH_2-CH(CH_3)_2$		
i	$-NH-COOC_2H_5$ *(6)*	$-CH_3$	194–195	hypnotic, muscle relaxant
k	$-NH-CO-NH-CH_2-COOC_2H_5$ *(6)*	$-CH_3$	192	muscle relaxant
		Y = $-N(COOC_2H_5)_2$		
l	$-NH-COOC_2H_5$ *(6)*	$-CH_3$	156–157	sedative, muscle relaxant
		Y = 		
m	$-NH_2$ *(6)*	$-H$	218–220	analgetic

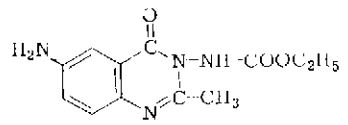
Compounds of this type show different behavior toward acylating agents. If both amino groups are free, the one at the benzene nucleus will be strongly preferred and



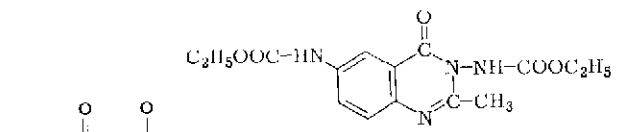
[7] Nitration of isatoic anhydride: *H. Kolbe*, J. prakt. Chem. (2) *30*, 477 (1884).

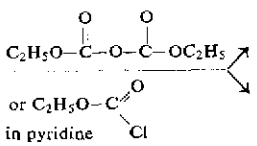
[8] Nitroacylanthranilic anhydrides: *M.T. Bogert*, J.Amer. chem. Soc. *27*, 649, 1305, 1327 (1905); *28*, 208, 884, 1449 (1906); *30*, 807 (1908).

will be acylated first (see Table 3, b). If the amino group at the hetero ring is acylated, as in *(15)* or in isomeric amines which carry the amino group at C-5, C-7, or C-8, not only will the free aromatic amino group be acylated on further acylation to give *(16)*, but addition of a second acyl group in the 3-position to give *(17)* occurs easily when an excess of the acylating agent is present.

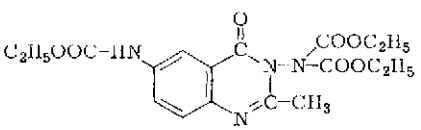


(15), see Table 3, c





(16), see Table 3, e



(17), see Table 3, e

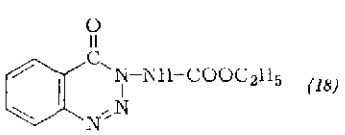
Urethanes of type *(16)*, which are soluble in aqueous alkali, become insoluble by double acylation *(17)*.

The bis(urethane) *(16)* exhibits pronounced sedative and muscle-relaxant action in animal tests [9]. The combination of these two properties should be of great interest to the clinician. Many hypnotics – especially the barbiturates – lead to sleep only after preliminary stimulation. In contrast, this compound relaxes the muscles just as in the process of falling asleep naturally.

The urethane group at the benzene ring is important for biological effectiveness. In *(15)* where it is missing, the compound is almost inactive. Compound *(17)* and the compound corresponding to *(16)* but with a free amino group in the 3-position, are almost equal to *(16)* in their activity. The position of the urethane group in the benzene ring can be changed without any great effect on the activity (see Table 3, d–g).

3-Aminobenzotriazinones

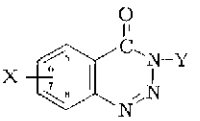
The first derivatives of 3-aminobenzotriazinone were prepared by *Heller* [3]. He obtained 3-(ethoxycarbonylamino)benzotriazinone *(18)* from anthranilic N^2-ethoxycarbonylhydrazide *(3)* with nitrous acid.



(18)

W. Wirth and *F. Hoffmeister* of our Elberfeld laboratories have found that this long familiar compound shows a pronounced but brief hypnotic action in animal tests [10]. However, its simultaneous strong emetic action prevents its use in clinical applications (see Table 4, e).

Table 4. 3-Aminotriazinones



	X and Y	M.p. [°C]	Activity
a	$-NH_2$	152–153	weakly hypnotic
b	$-NH-CO-CH_3$	199–200	almost inactive
c	$-NH-CO-$	225 (hydrochloride)	weakly hypnotic
d	$-NH-CO-CH_2-$	230 (decomp.)	weakly hypertensive
e	$-NH-COOC_2H_5$	150–151	briefly strongly narcotic, strongly emetic
f	X = $-CH_3$ *(7)*	172–173	narcotic, induces muscles spasms
g	X = $-SO_2-NH_2$ *(6)*	223–225	inactive
h	X = $NH-COOC_2H_5$ *(6)*	191–192	narcotic and muscle relaxant, weakly diuretic
i	$-NH-COO-CH_2-CH=CH_2$	98–99	narcotic and muscle-relaxant, strongly emetic
k	X = Br *(6)*	102–103	narcotic, weakly analgetic, induces muscle spasms
l	$-NH-COO-CH_2-CH_2-OH$	137–138	muscle relaxant, anticonvulsive, analgetic
m	$-NH-COO-CH_2-CH_2-OCH_3$	84–86	prolonged narcotic
n	$-NH-CS-OC_2H_5$	150–152	almost inactive
o	$-NH-CS-NH-CH_2-CH=CH_2$	173	prolonged narcotic
p	$-NH-SO_2-$	220–222	weakly anticonvulsive
q	$-N(CH_3)-COOC_2H_5$	95–96	narcotic
r	$-N(CH_2-COOC_2H_5)-COOC_2H_5$	111–112	narcotic, induces muscle spasms
s	$-N(CH_3)-SO_2-CH_3$	158–159	narcotic, weakly diuretic and anticonvulsive
t	$-N(CH_3)_2$	117	analgetic
u	$-N$	146–147	analgetic
v	$-N$	118–119	weakly analgetic
w	$-N$	199–200	good analgetic properties, antipyretic
x	X = $-CH_3$ *(7)*	149–150	analgetic
y	$-N$	180–181	weakly analgetic
z	$-N$	158–159	weakly analgetic

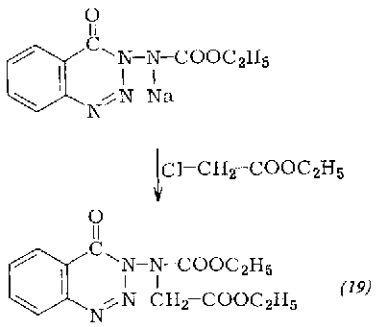
The hydrogen atom of the 3-acylamino group can be substituted by alkali, a property it shares with the acylated 3-aminoquinazolones described above. The stable alkali salts are suitable for preparations for injection. They are good starting materials for alkylation and acylation at the NH-group of the side chain, *e.g. (19)* (see Table 4, q–t).

Modification of the alcohol in the urethane group of compound *(18)* generally does not lead to more easily

[9] *K. Stoepel* and *G. Kroneberg*, Naunyn-Schmiedebergs Arch. exp. Path. Pharmak. *241*, 512 (1961).

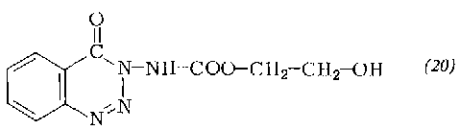
[10] The parent compound, benzotriazin-4-one, is claimed to have some sedative effect: *S. M. Gadekar* and *E. Ross*, J. org. Chemistry *26*, 613 (1961).

tolerated benzotriazinones (see *e.g.* Table 4, i). Only when a hydroxyl group is introduced into the side chain a usable drug is obtained *(20)*. Hydroxyethoxycarbonylhydrazine (made from glycol carbonate and hydrazine [11]) was treated with isatoic anhydride and the triazinone ring closed with nitrous acid (see Table 4, b).



(19)

Even though the introduction of the hydrophilic group results in the loss of the short-acting hypnotic activity, a very active muscle-relaxant compound is obtained.

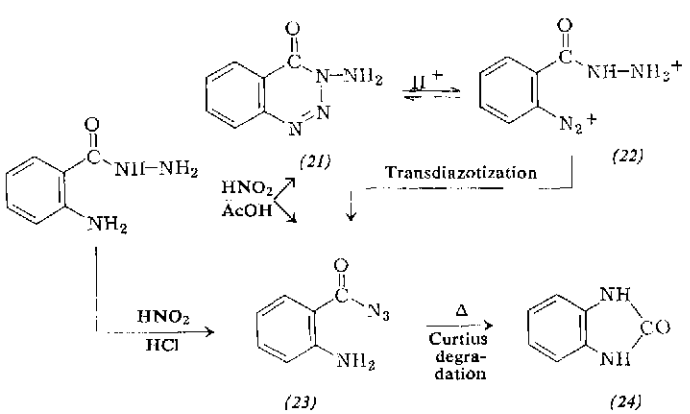


(20)

The latter can be used for treatment of severe cases of tension and for certain mental diseases (*W. Wirth, F. Hoffmeister*).

With nitrous acid, all the anthranilic N^2-acylhydrazides close the triazinone ring in a smooth reaction and in good yield. There are difficulties, however, with anthranilic hydrazides derived from free hydrazine or from monoalkyl- or monoarylhydrazines.

Thus, treatment with nitrous acid of free anthranilic hydrazide (its diazotization has already been investigated by *Heller* [12]) yields either *o*-aminobenzazide *(23)* alone or a mixture of this compound with 3-aminobenzotriazin-4-one *(21)*, depending upon the strength of the acidic solution (acetic or hydrochloric acid).

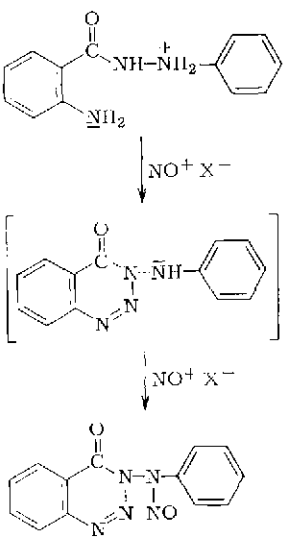


(21) *(22)* *(23)* *(24)*

In strongly acidic solution, compound *(21)* is in equilibrium with the diazonium hydrazide *(22)*. Transdiazotation of *(22)* yields the azide *(23)*. At 100 °C, a Curtius degradation takes place, isocyanate is formed, and the benzimidazolone *(24)* is obtained from the azide by ring closure with the *o*-amino group.

The aldehyde and ketone derivatives of 3-aminobenzotriazin-4-one, like the hydrazones of 3-aminoquinazolones [13], do not show any muscle-relaxant, sedative, or hypnotic properties and will therefore not be considered here.

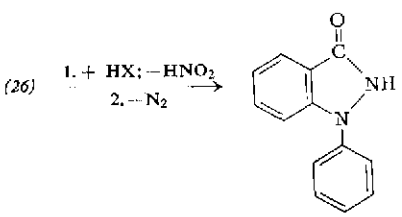
Anthranilic hydrazides derived from monosubstituted aliphatic or aromatic hydrazines react differently. Thus, 3-nitrosoanilinobenzotriazin-4-one, for example, is formed from anthranilic N^2-phenylhydrazide *(25)* with one mole of nitrous acid or even less. Thus, closure of the triazinone ring takes place simultaneously with a nitrosation at the NH group in the side chain *(26)*.



(25) *(26)*

In acidic solution, anthranilic hydrazides undoubtedly react with nitrosating agents at the aromatic amino group first, since under acidic conditions, the latter is the nitrogen protonated to the least extent. The basicity of the hydrazine nitrogen atom that is not attached to the carbonyl group is strongly reduced by intramolecular ring closure of the diazonium group with the hydrazide group. The 3-aminobenzotriazinones are not basic, their 3-amino group is less protonated in acidic solution than an aromatic amino group and therefore undergoes further reaction with nitrosyl ions instantaneously. Accordingly, only products of type *(26)* could be isolated from 3-alkyl- and 3-arylaminobenzotriazinones.

The nitrosoaminobenzotriazinones are relatively stable compounds. It was possible to obtain analytically pure samples by dissolving the crude products in dimethylformamide and reprecipitating them with water. They have the rather rare arrangement of six hetero atoms linked together. They give off nitrous acid in acidic solution or on boiling with alcohol. The products rearrange to substituted indazolones, *e.g.* compound *(27)*,



(26) *(27)*

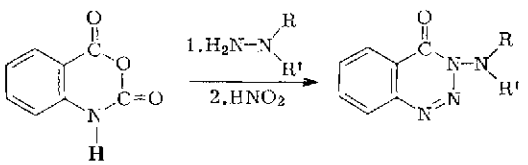
[11] *R. Delaby, R. Damiens* and *M. L. Capnau*, C. r. hebd. Séances Acad. Sci. *246*, 3353 (1958).

[12] *G. Heller*, J. prakt. Chem. (2) *111*, 36 (1925); *116*, 9 (1927).

[13] *C. Thode*, J. prakt. Chem. (2) *69*, 100 (1904).

via intramolecular nucleophilic substitution and elimination of nitrogen [14].

Nitrosation of 3-aminobenzotriazinones does not take place if the free electron pair of the 3-amino group is involved in an inductive or mesomeric interaction with electron attracting groups, *e.g.* acyl, nitrophenyl, or pyridinium groups. Anthranilic hydrazides derived from *N,N*-disubstituted hydrazines, H_2N-NR_2, also fail to undergo nitrosation. It is thus possible to obtain 3-(dialkylamino)benzotriazinones *(28)* from *N*-amino compounds of secondary bases, isatoic anhydride, and nitrous acid. The *N*-amino compounds of cyclic bases can also be used for this reaction (see Table 4, t–z).



(28)

$R = R' = CH_3$

$R + R' = -(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-S-(CH_2)_2-$

In this class of compounds, good analgetic action in animal and clinical tests was obtained (*W. Wirth, F. Hoffmeister*) with 3-morpholinobenzotriazin-4-one (see Table 4, u). This compound corresponds to formula *(28)* with $R + R' = -(CH_2)_2-O-(CH_2)_2-$. The compound does not belong to the group of "strong" analgetics of the morphine type, but is rather to be considered as a "run-of-the-mill" analgetic to be used in combination with other pain-relieving components, if necessary. Its excellent tolerance must be emphasized.

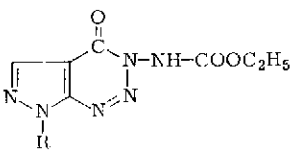
Detection of 3-morpholinobenzotriazinones in blood and tissue fluids is simple, since it is an intramolecular diazonium compound. Reversing the ring closure reaction, benzotriazinones are cleaved by strong acids and couple with aromatic amines, forming dyes which can be measured colorimetrically (*J. Pütter*). Since 3-morpholinobenzotriazinone is not soluble in water, the blood level attainable depends upon the pharmaceutical formulation.

Substitution at the benzene nucleus of 3-morpholinobenzotriazinone was carried out successfully in many instances. The products, however, did not offer any significant advantages over the non-substituted compound.

N-Aminomorpholine is required for the synthesis of 3-morpholinobenzotriazinone. Usually, the *N*-amino compounds of secondary amines are prepared by nitrosation of the amines, followed by reduction. Since several papers dealing with the carcinogenic properties of *N*-nitrosodialkylamines [15] appeared while our studies were in progress, we have eliminated these intermediates from the commercial process.

We have discovered, in collaboration with the Anorganisch-Wissenschaftliche Abteilung (Inorganic Research Division) of our company (*H. Kohnen, H. J. Abendroth*), that continuous reaction of sodium hypochlorite, ammonia and morpholine in a Raschig-type synthesis yields aqueous solutions of *N*-aminomorpholine. These solutions can be used in the synthesis of 3-morpholinobenzotriazin-4-one without isolating the base.

The reactions described here can also be applied for synthetizing heterocyclic *o*-aminocarboxylic acids. Compounds of type *(29)* may be obtained from 1-aryl- or 1-alkyl-5-aminopyrazole-4-carboxylic hydrazides by reaction with diethyl pyrocarbonate and ring closure with nitrous acid.



(29), R *e. g.* $-C_6H_5$, $-CH_2-CH_2-OH$

Tables 2–4 show characteristic representatives of the quinazolones and benzotriazinones we have prepared. A total of well over 200 derivatives has been tested.

We wish to express our gratitude to the Pharmacological Analysis Laboratory of the Eberfeld Works, especially to Dr. M. Bock, Prof. Dr. W. Wirth, Prof. Dr. H. G. Kroneberg, Dr. F. Hoffmeister, and Dr. K. Stoepel.

Received, May 16th, 1962 [A 237/62 IE]

[14] *A. König* and *A. Reissert*, Ber. dtsch. chem. Ges. *32*, 782 (1899); *C. Thode*, J. prakt. Chem. (2) *69*, 92 (1904).

[15] *H. Druckrey* et al., Naturwissenschaften *48*, 134 (1961); additional references are given there.

Polycondensation Dyes

A New Principle for the Preparation of Wash-Fast Cotton Dyeings

BY DR.-ING. K. SCHIMMELSCHMIDT, DR. HERMANN HOFFMANN, AND DR. E. BAIER

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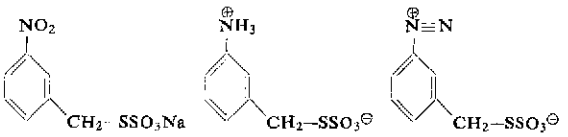
Dyes which contain only thiosulfate residues as water-solubilizing groups are readily polycondensed on cellulose under mild conditions in the presence of condensing agents such as sodium sulfide to give insoluble, high molecular-weight dyes. This type of fixation leads to wash-fast dyeings and, in contrast to reactive dyes, involves no reaction with the fiber. The preparation and application of the dyes are described.

1. Introduction

Alkali salts of *S*-alkyl thiosulfates (Bunte salts) may be transformed into disulfides under various conditions. This reaction should serve to improve the wetfastness of direct dyes, in which part of the sulfonic acid groups is replaced by thiosulfate groups. We have prepared several such dyes by treatment of thiosulfato-diazo compounds with coupling components customarily used for the synthesis of substantive azo dyes.

Although aliphatic amines containing thiosulfate residues were known [1], the corresponding aromatic, diazotizable amines were lacking. (The known compound *o*-aminophenylthiosulfuric acid is transformed



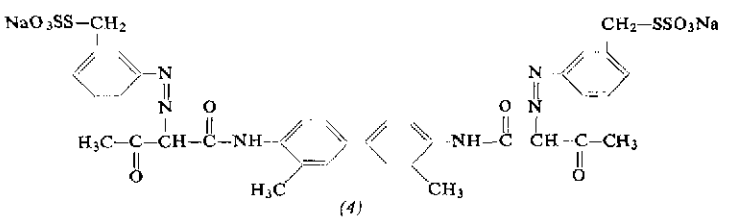
(1) *(2)* *(3)*

into non-coupling benzothiadiazole on diazotization [2].) We were able to prepare such amines by reduction of the corresponding nitro compounds with iron and iron sulfate and to isolate them in pure form. Thus, *m*-aminobenzylthiosulfuric acid *(2)* was obtained from the sodium *m*-nitrobenzylthiosulfate (1), and was then transformed into *m*-diazobenzylthiosulfuric acid *(3)*.

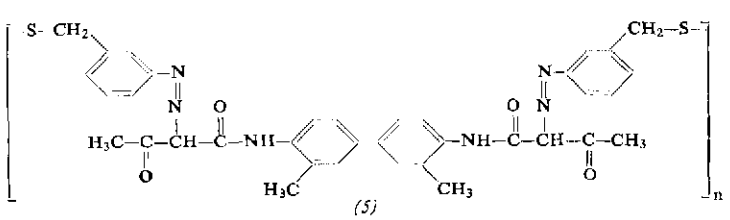
Coupling of compound *(3)* with derivatives of 2-amino-5-naphthol-7-sulfonic acid yielded substantive dyes, the dyeings of which on cotton exhibited distinctly better wash-fastness than dyeings with analogous dyes containing sulfo groups instead of thiosulfate residues. Compound *(3)* was also coupled with 4,4'-bis(aceto-acetylamino)-3,3'-dimethyldiphenyl (®Naphtol AS-G) to give dye *(4)*, the water solubility of which was due only to its thiosulfate groups. Cotton dyeings with *(4)* from alkaline baths were yellow; they had better wash-fastness than dyeings with dyes which contained sulfo groups along with thiosulfate groups. They achieved the same wash-fastness as vat dyeings.

The water-soluble Bunte salt dyes were plainly transformed under the conditions of dyeing into water-insoluble disulfides; the structure of the latter corresponds either to polymer chains with the repeating unit *(5)* or to cyclic oligomers.

Starting out from this observation, we developed a group of new dyestuffs that are easily fixable on cotton.



(4)



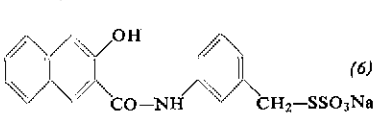
(5)

[1] German Patent 869066 (1953), Bobingen AG., inventor: *P. Schlack*.

[2] German Patent 120504 (1900), Clayton Aniline Comp.

2. Preparation of Bunte Salt Dyes

For reasons based on industrial applications, we prepared preferentially dyes containing several thiosulfate residues. Dyes with only one such group are practicable only in exceptional cases. Bunte salt dyes are obtained by coupling diazo compounds containing thiosulfate



(6)

groups with polyfunctional components free of sulfo groups, *e.g.* with Naphtol AS-G, Naphtol AS-FGGR, or the naphthol derivative *(6)* [derived from *(2)* and 2-hydroxy-3-naphthoic acid].

Another method of synthesis of polyfunctional Bunte salt dyes entails the condensation of aliphatic or aromatic amines containing thiosulfate groups with dyes containing reactive halogen atoms, *e.g.* dyestuff sulfonyl chlorides or carbonyl chlorides. Among the products so obtained are Inthion Brilliant Blue I5G®, and other blue and green dyes.

The Bunte salt dyes previously described [3, 4] for dyeing cellulose acetate are not suitable as polycondensation dyes.

3. Properties of Bunte Salt Dyes

The properties of the dyes containing thiosulfate groups are largely determined by these groups. They give practically all the reactions of Bunte salts.

There are several possibilities for the condensation of Bunte salts to disulfides [5]. Treatment with sodium sulfide as condensing agent proceeds very quickly and under the mildest conditions [6]. This affords disulfides in quantitative yield.

$$2\ R{-}SSO_3Na + Na_2S \longrightarrow R{-}S_3{-}R + 2\ Na_2SO_3$$

$$R{-}S_3{-}R + Na_2SO_3 \xrightarrow{(Na_2S)} RSSR + Na_2S_2O_3$$

In contrast, with other condensing agents water-soluble by-products are often formed; for example, with aqueous alkali, sulfinic acids are produced [7]. Since the wash-fastness of the dyeings is already decreased by a low content of water-solubilizing groups, the Bunte salt groups must be converted into the disulfides as completely as possible and without formation of water-soluble by-products. For this reason also, condensation in the presence of sodium sulfide is most suitable for fixation of the dye.

The aliphatic disulfide groups arising from the polycondensation are stable to sodium sulfide, in contrast to aromatic disulfide groups; once they are polycondensed, the dyes therefore remain insoluble in water even under the action of excess sodium sulfide. In this respect, they differ from sulfur dyes, which are transformed by sodium sulfide into water-soluble mercaptides.

Bunte salt dyes are also suitable for purposes other than polycondensation on cellulose. For example, acid hydrolysis leads to thiols [8], which generally separate in readily filterable form.

$$RSSO_3Na + H_2O \xrightarrow{H^{\oplus}} RSH + NaHSO_4$$

The thiols are insoluble in water and are stable to atmospheric oxygen; they can be utilized as disperse dyes or pigments. In aqueous alkali, they dissolve as mercaptides, which are readily oxidized to insoluble disulfides by atmospheric oxygen. Their solutions are thus suitable for the preparation of wash-fast dyeings and printing on cotton and rayon.

In aqueous media, alkali cyanides readily convert Bunte salt dyes into isothiocyanates, even at room temperature [9],

$$RSSO_3Na + NaCN \rightarrow RSCN + Na_2SO_3$$

These can react further to form disulfides or to effect ring closure with neighboring groups.

4. Application of Bunte Salt Dyes

Five pad-dyeing procedures have been developed for the application of the Bunte salt dyes; these may be divided into one-bath and two-bath methods. All share the principle of color fixation in alkaline to neutral medium in the presence of sulfur compounds.

In the one-bath methods, the padding liquors contain additives which generate alkali sulfides at elevated temperatures. After drying, the dyed material is steamed for one or two minutes (one bath pad steaming method) or heated dry for a short time (one-bath pad thermofixing method) to achieve fixation.

In the two-bath methods, the pad-dyeing liquor contains only the usual additives, such as urea and thickeners. For fixation, the dried dyeings are either aftertreated on a jig at 30–60 °C with a relatively dilute solution of sodium sulfide (two-bath pad jig method), or treated with a sodium sulfide solution of higher concentration for a short time at room temperature [air exposure of 30–40 seconds (two-bath pad air exposure method) or skeining of the goods and short dwell in the skein (two-bath skein method)]. Fixation is practically quantitative in all the methods, so that the dyeings require only a short rinsing or soaping operation. The most interesting process is the two-bath air-exposure padding method, because here no energy need be supplied for fixation and because the fixation time is so short that a high throughput of goods is possible.

The pad dyeings can also be fixed in acid medium with formaldehyde or with substances that evolve formaldehyde. In this process, the thiosulfate groups are probably first transformed into SH-groups, which then react further with formaldehyde to form thials or undergo ring closure with neighboring groups to yield heterocyclic compounds. By this method, cotton can be dyed and rendered wrinkle-resistant in a single operation. The polycondensation dyes act principally as padding dyes in the dyeing of cotton. Because of their low substantivity, they are extracted only slightly by unmordant cotton from dilute solutions. In contrast, wool and polyamide fibers are dyed strongly from dilute solution. The reactions in the dyeing of wool with Bunte salt dyes have recently been described [10]. The resulting dyeings have excellent fastness.

Received, July 5th, 1962 [A 247/65 IE]

[3] US.-Pat. 2283326 (1942), Ges. Chem. Ind., Basel, inventor: *F. Felix* and *W. Müller*.

[4] Brit. Pat. 510453 (1939), Ges. Chem. Ind., Basel, inventor: *F. Felix* and *W. Huber*.

[5] *Houben-Weyl:* Methoden der organischen Chemie. 4th Ed., Thieme, Stuttgart 1955, vol. IX, p. 67.

[6] German Patent 928733 (1955), Farbwerke Hoechst, inventor: *P. Schlack*; *G. Spielberger*, Kautschuk *13*, 137 (1937).

[7] *A. Dornow*, Ber. dtsch. chem. Ges. *72*, 568 (1939).

[8] *U. Weiss* and *H. Stekol*, J. Amer. chem. Soc. *72*, 1687 (1950).

[9] *H. B. Footner* and *S. Smiles*, J. chem. Soc. (London) *1925*, 2887.

[10] *B. Milligan* and *J. M. Swan*, Textile Res. J. *31*, 19 (1961); *F. Osterloh*, Angew. Chem. *74*, 699 (1962).

Low-Temperature Polymerization of Ethylene

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A two-component organometallic catalyst of composition $CH_3TiCl_3 \cdot CH_3AlCl_2$ effects high-speed polymerization of ethylene in the presence of chlorinated hydrocarbons at low temperatures. The catalyst does not undergo any alteration in the process. In contrast to the Ziegler catalysts, the titanium remains quadrivalent. Olefins of low molecular-weight and with branched structures are produced. It proved possible to isolate the primary products of the polymerization at −50 to −100 °C and to elucidate the mode of their formation from a knowledge of their structures. The findings are incompatible with either a cationic or anionic reaction mechanism. A novel type of mechanism is proposed, whereby the catalyst is supposed to have an ionic structure and molecular growth proceeds via π-complex formation of the olefin with the titanium cation. The formation of ethylene/olefin copolymers is also discussed.

Introduction

Low-pressure polymerization of ethylene according to the method of *Ziegler* and co-workers [1] yields high molecular-weight, practically unbranched polyethylenes (polythenes). The theory and the mechanism of this polymerization have been developed by several authors [3–6], particularly by *Natta* [2]. An anionic coordination mechanism agrees best with the experimental results. The alkyl residues attached to the metal atom of the catalyst react as anions with the monomeric olefin without separation of the growing chain from the catalyst. The mechanism, therefore involves a fast reaction of the metal-carbon bond with the olefin. The same phenomenon occurs in the known growth reaction with aluminum alkyls, albeit slowly [7].

Among the many catalyst systems proposed by *Ziegler*, those using aluminum alkyls and titanium chlorides are the main ones used in industry. Saturated aliphatic hydrocarbons are employed as solvents and dispersants for the catalyst and the polymeric products.

In 1955, while trying to elucidate the function of catalytically effective systems and to develope an industrial polyethylene process, we made the surprising observation that the expected high molecular-weight, solid polyethylene is formed in octane in a smooth polymerization reaction when using a catalyst made from titanium(IV)-chloride and diethylaluminum chloride (Table 1, Column A), whereas polyethylene oils of low molecular-weight and with branched structures are rapidly produced, even below room temperature, when chloroform is used as solvent (Table 1, Column B) [8].

Table 1. Atmospheric pressure polymerization of ethylene with titanium(IV) chloride and dialkylaluminum chloride as catalyst

	A	B
Valence of titanium in the active catalyst	3 + 4 or 3	only 4
Composition and solubility of catalyst	heterogeneous, undissolved	homogeneous, dissolved
Reaction medium	hydrocarbons	aliphatic chlorinated hydrocarbons
Polymerization temperature (optimum region)	20 to 100 °C	−100 to 20 °C
Properties of polymeric product	solid	liquid
	melting point > 128 °C	pour point *ca.* −40 °C
	high molecular-weight	low molecular-weight
	straight chain	branched
End groups	alkyl residues of catalyst	no catalyst fragments

Further investigation of this unusual course of reaction led to the conclusion that a two-component organo metal system of the above composition is also effective as a catalyst for the polymerization of ethylene, even if the titanium component is not reduced to titanium(III)-chloride, but exists as a titanium(IV) compound dissolved homogeneously with the aluminum component.

A two-component catalyst which fulfills these conditions allows ethylene to dimerize even at −100 °C when chlorinated hydrocarbons are employed as solvents. The study of this polymerization reaction gave an

[1] *K. Ziegler* et al, Angew. Chem. *67*, 541 (1955).

[2] *G. Natta* et al., Angew. Chem. *69*, 213 (1957); Chim. e Ind. *39*, 1032 (1957).

[3] *H. N. Friedländer* and *K. Oita*, Ind. Engng. Chem. *49*, 1896 (1957).

[4] *G. Bier*, Kunststoffe *48*, 354 (1958).

[5] *F. Patat* and *Hj. Sinn*, Angew. Chem. *70*, 496 (1958).

[6] *H. Uelzmann*, J. Polymer Sci. *32*, 457 (1958).

[7] *K. Ziegler* et al., Angew. Chem. *64*, 323 (1952); Liebigs Ann. Chem. *629*, 121 (1960).

[8] Belg. Pat. 550429 (1956), Farbwerke Hoechst AG.

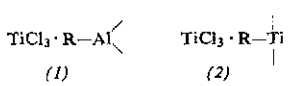
insight into a mechanism of olefin polymerization which displays characteristics that are new and have not been previously discussed.

Valence of Titanium

Typical two-component systems composed of titanium-(IV)-chloride and aluminum alkyls are not stable. This is especially true when two or three alkyl groups are attached to the aluminum and each of these alkyl groups contains two or more carbon atoms. When the components are mixed (before or during the polymerization), a reaction takes place which leads, via the soluble intermediate step of alkyltitanium(IV) halides, to insoluble titanium(III) chloride (Equation a) [9].

$$\underbrace{TiCl_4 + R_2AlCl}_{C} \rightleftarrows \underbrace{RTiCl_3 + RAlCl_2}_{B} \rightarrow \underbrace{TiCl_3 + RAlCl_2}_{A} + R\cdot \quad (a)$$

Titanium(III)chloride separates as a brown to red-brown precipitate and, in the complex with the aluminum alkyls, must be regarded as the true catalyst for the anionic polymerization of ethylene and α-olefins. The alkyltitanium trichloride, formed as a soluble intermediate in reaction (a), is also activated by the titanium trichloride to function as a polymerization catalyst, so that two active systems are assumed to participate in the anionic polymerization according to *Ziegler* [9].



(1) *(2)*

Both two-component catalysts are heterogeneous systems, with the titanium components at least partly in the trivalent form, as in *(2)*. So far no observations have been reported to substantiate the conclusion that the two-component systems B and C (Eq. a) as such (*i.e.*, in the absence of solid catalyst components) are able to polymerize ethylene. Experimental investigation of this problem encounters difficulties when the commonly employed aluminum alkyls (alkyl = ethyl or higher residue) are used, because the reaction C → A (Eq. a) occurs rapidly even at room temperature, and B is only a short-lived intermediate. At lower temperatures, ligand exchange between titanium and aluminum no longer takes place, and the transformation C → B fails to occur.

Two-component systems containing methylaluminum compounds proved very useful in our investigations. These systems were investigated by *C. Beermann* and ourselves. They make it possible to prepare pure methyltitanium trichloride [9], since the double transformation C → B proceeds with normal speed, while the decomposition B → A is strongly retarded because of the strength of the Ti–CH_3 bond (Equation b).

$$\underbrace{TiCl_4 + (CH_3)_2AlCl}_{C} \overset{\text{fast}}{\rightleftarrows} \underbrace{CH_3TiCl_3 + CH_3AlCl_2}_{B} \xrightarrow{\text{slow}}$$

$$\underbrace{TiCl_3 + CH_3AlCl_2}_{A} + CH_3\cdot \quad (b)$$

[9] *C. Beermann* and *H. Bestian*, Angew. Chem. *71*, 618 (1959).

If titanium tetrachloride is treated in a solvent with dimethylaluminum chloride, ligand exchange takes place rapidly and leads to an equilibrium between systems C and B, recognizable from the color of methyltitanium trichloride in the solution. The position of the equilibrium between systems C and B has meanwhile been investigated by others ($K_{eq}^{20} \approx 1$) [10].

These soluble systems, in which the titanium components exist in tetravalent form, exhibit no catalytic activity towards ethylene when dissolved in saturated aliphatic hydrocarbons below −20 °C. At higher temperatures (*e.g.*, room temperature), the systems with tetravalent titanium are unstable in the presence of ethylene. In this temperature region, the ethylene probably reacts with the Ti CH_3 bond, facilitating the transformation B → A and making any system containing $TiCl_3$ effective.

In chlorinated hydrocarbons (methyl chloride, methylene chloride, chloroform, chlorobromomethane, *etc.*), the soluble system made from titanium tetrachloride and dimethylaluminum chloride has a surprisingly high activity as polymerization catalyst, especially for ethylene. The mode of action of these multicomponent organometallic catalysts containing tetravalent titanium constituents is, however, different from that of a *Ziegler* catalyst system (see Table 1).

Active Two-Component Organometallic System Containing a Tetravalent Titanium Component

An equimolar mixture of titanium(IV) chloride and dimethylaluminum chloride in methylene chloride is an equilibrium mixture of four components: $TiCl_4$, CH_3TiCl_3, $(CH_3)_2AlCl$, and CH_3AlCl_2.

Mixing of the starting components and the double decomposition involving ligand exchange (Eq. b, C → B) probably do not lead to preferred, or even stable, two-component complexes. If such complexes, *e.g.* between methyltitanium(IV) chloride and methylaluminum dichloride, are present, then certainly they are only loosely bound and in equilibrium with the components.

We have been able to clarify the question of the nature of the true catalyst in this equilibrium mixture by means of the following considerations and experiments.

1. The four components in a 0.04 M concentration in methylene chloride do not affect ethylene passed through the solution.

2. The following combinations are possible as two-component catalysts:

a) Titanium(IV) chloride/dimethylaluminum chloride
b) Titanium(IV) chloride/methylaluminum dichloride
c) Titanium(IV) chloride/methyltitanium(IV) chloride
d) Methyltitanium(IV) chloride/dimethylaluminum chloride
e) Methyltitanium(IV) chloride/methylaluminum dichloride

A further possibility, a mixture of mono- and dimethylaluminum chlorides, was excluded from the outset, because this mixture (known as "sesquichloride") is inactive under the present conditions, just like aluminum chloride.

[10] *H. P. Groenewege*, Z. physik. Chem. (N.F.) *18*, 147 (1958).

Testing of the two-component systems (a) through (e) was made possible by the observation that the rate of attainment of the equilibrium

$$TiCl_4 + (CH_3)_2AlCl \rightleftarrows CH_3TiCl_3 + CH_3AlCl_2 \qquad (c)$$

is dependent on temperature.

Below −50 °C, equilibrium does not occur within the period of time allotted for the experiment.

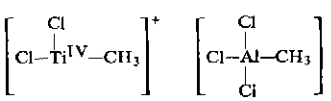
The two-component systems were compared at −70 °C with a catalyst mixture of titanium(IV) chloride and dimethylaluminum chloride prepared in methylene chloride at 20 °C. The components of the system to be tested were dissolved in methylene chloride previously cooled to −70 °C.

This investigation showed that combinations (a) through (c) are not the actual catalysts for the polymerization of ethylene. Mixture (d) is weakly active. However, combination (e) proved to be a very effective catalyst, which surpassed even the activity of the reference mixture.

Polymerization of ethylene at −70 °C in methylene chloride containing dissolved methylaluminum chloride begins immediately after the addition of methyltitanium(IV) chloride dissolved in methylene chloride. In contrast, a solution of titanium(IV) chloride and dimethylaluminum chloride in methylene chloride, prepared under the same conditions, remains completely colorless on passing in ethylene. Only after induction period does an incipient yellow and red coloration denote the transformation to the active system, and the ethylene being passed in begins to polymerize with increasing speed.

Accordingly, the combination CH_3TiCl_3/CH_3AlCl_2 is to be regarded as the active catalyst. Since either component alone is not effective, the active system must be a complex. The fact that methylaluminum dichloride dissolves better in hydrocarbons when mixed with an equimolar quantity of methyltitanium(IV) chloride is a further indication of the existence of a complex [11].

One can only speculate as to the constitution of this catalytically effective complex, since it cannot be isolated. We prefer an ionic complex of structure *(3)*, rather than other structures with Cl or CH_3 bridges between the titanium and aluminum [2, 5].



(3)

Composition of the Catalyst

The anionic olefin polymerization according to *Ziegler* is catalyzed by numerous multicomponent systems. The composition of these catalysts can also be varied within wide limits. Our two-component organometallic system must consist of alkyltitanium(IV) chloride and alkylaluminum dichloride. Only small deviations from this composition are permitted if the described catalytic effect for ethylene polymerization is not to be lost. For the effect of the mole ratio $RTiCl_3:RAlCl_2$, see below (Table 5).

[11] *R. Graf*, unpublished.

The combination $CH_3TiCl_3{\cdot}(CH_3)_2AlCl$ has considerably lower activity. If methylaluminum dichloride is replaced by trimethyl aluminum, the system is ineffective. The combination $CH_3TiCl_3{\cdot}AlCl_3$ is also only weakly active; this may be due to the low solubility of aluminum chloride in methylene chloride at −50 °C.

The alkyl residue of the organometallic system has only a small effect. In place of methyl compounds, ethyl compounds can also be used. The methyl compounds, however, are preferred because of their greater stability.

The catalyst becomes ineffective if another metal from the adjoining groups of the periodic system is introduced in place of the titanium. Furthermore, substitution of the aluminum component by alkylborons, boron trifluoride, stannic chloride, antimony pentachloride, and other compounds of the Friedel-Crafts catalyst type also yields ineffective combinations. Combinations with titanium tetrachloride (*e.g.* $TiCl_4{\cdot}AlCl_3$) are also inactive, if the latter has not been converted, through double decomposition with an organometallic component, into an alkyltitanium(IV) chloride.

Low-Temperature Polymerization of Ethylene

The experiments described below were carried out between −60 and −100 °C. Below −100 °C, the catalyst activity drops sharply, and above −50 °C, the primary products of the ethylene polymerization are converted via a secondary polymerization into highly branched, partly oily olefins (see Table 2). Apart from this, the temperature range between −60 and −100 °C is suited for elucidation of the structure of the catalyst and the mechanism of the polymerization reaction for the following reasons:

1. It has already been shown that below −60 °C, ligand exchange in the catalytically effective two-component system (*e.g.*, CH_3 for Cl) practically disappears. Moreover, the active organo metallic system remains unchanged after many hours of reaction and high conversion of ethylene, with the tetravalent titanium and the original alkyl groups still present.

2. Ethylene polymerization between −60 and −100 °C leads to products of chain length C_4 to C_{10}, which can be analyzed quantitatively, and as primary products permit deductions as to the course of the polymerization.

As catalyst, we used either a mixture of titanium(IV) chloride and dimethylaluminum chloride (or "sesquichloride"), prepared at room temperature, or with still better success, a mixture of methyltitanium(IV) chloride and methylaluminum dichloride. Both systems were dissolved in methylene chloride or in another chlorinated hydrocarbon that remains liquid in this temperature region. For optimum utilization of the activity of the methyltitanium(IV) chloride methylaluminum dichloride system, the components were introduced separately into the solvent, which had previously been cooled to the polymerization temperature. The clear solutions of the catalyst in methylene chloride (in the standard experiment 0.04 M in both components) are pale yellow-red. On passing in ethylene, or on addition of another olefin, the color turns dark red, and deepens so much that the solution in a liter vessel is no longer transparent. The strong deepening of color is retained during the

polymerization. If, at a catalyst concentration of 0.04 M, the ethylene is admitted at the same rate at which it is consumed, *ca.* 200 g of polymerized olefin is formed per hour per liter of solvent. Thus, the level of catalyst performance is about the same as that of the *Ziegler* catalysts at 70 °C.

In this low-temperature region, the choice of solvent is limited by the melting point of same. Several chlorinated hydrocarbons were examined (see Table 4). A significant dependence of the catalyst activity on the solvent used may be seen from the amounts of ethylene converted. The best results were obtained with methylene chloride

Table 4. Effect of solvent on catalyst activity. (Catalyst and reaction conditions, see heading of Table 2; reaction temperature −70 °C).

Solvent	Ethylene conversion [%]	Yield of polymerized olefin [% of converted C_2H_4]					2-Ethyl-1-butene [% of C_6 fraction]	2-Ethyl-1-hexene [% of C_8 fraction]
		C_4	C_6	C_8	C_{10}	$> C_{10}$		
Methylene chloride	83	14	30	15	5	36	70	77
1,1-Dichloroethane	77	13.5	22	13	6	45.5	60	68
Chlorobromomethane	86	12	29	16	6	37	75	78
Chloroform	45	16.5	29	20	8	26.5	60	80
Methyl chloride	65	19	29	19	8.5	24.5	62	71
Ethyl chloride	54	*ca.*28	20	14	6.5	31.5	44	62
n-Butyl chloride	39	19	29.5	16,5	10	25	not detd.	70
Trichloroethylene	26	19	29	17	11	24	40	59
1,1-Dichloroethylene	37	19	22	20	10	29	38	60
Chlorodifluoromethane	*ca.* 45	6.5	22	18	9	44.5	53	68
100 ml of CH_2Cl_2 + 300 ml of pentane	35	18.5	28.5	23	11.5	18.5	45	62

Tables 2–6 show results. The polymerization temperature (Table 2) influences the rate of polymerization and the composition (degree of polymerization and distribution) of the products very strongly.

Table 2. Effect of temperature on the polymerization of ethylene with $TiCl_4{\cdot}(CH_3)_3Al_2Cl_3$ in 400 ml of methylene chloride (0.045 M Ti, 0.09 M Al, 100 g of C_2H_4 per hour). Duration of experiment 6 hours

Temp. [°C]	Ethylene conversion [%]	Yield of polymerized olefin [% of converted C_2H_4]					2-Ethyl-1-butene [% of C_6-fraction]	2-Ethyl-1-hexene [% of C_8-fraction]
		C_4	C_6	C_8	C_{10}	$> C_{10}$		
−50	98	4	6	4.5	3	82.5	31	38
−60	97	7	11	9	5	68	56	65
−70	83	14	30	15	5	36	70	77
−80	72	24	39	14	3.5	19.5	74	80
−90	35	51	36	7	1.5	4.5	73	80
−100	13	65	35	—	—	—	70	—

Table 2 shows that the conversion of ethylene increases rapidly with increasing temperature, and that the fraction of low polymeric olefins decreases at the same time in favor of the higher ones.

Table 3 shows the course of the polymerization at −70 °C as a function of time. The activity of the catalyst is so great that in the first hour, the ethylene conversion amounts to *ca.* 90 %. Towards the end of the reaction, the activity falls, owing to the increase in polymeric olefins. The composition of the product also changes as the reaction progresses: the C_4–C_{10} olefins increase while the products with over ten carbon atoms decrease.

Table 3. Ethylene conversion and composition of products after various reaction times at −70 °C. (Catalyst and reaction conditions, see heading of Table 2)

Reaction time [hours]	Ethylene conversion [%]	Yield of polymerized olefin [% of converted C_2H_4]					2-Ethyl-1-butene [% of C_6 fraction]	2-Ethyl-1-hexene [% of C_8 fraction]
		C_4	C_6	C_8	C_{10}	$> C_{10}$		
1	92	10	9	3	2	76	45	—
3	92	13	20	9	5	53	60	75
3.5	90	13	24	9.5	5	48.5	65	74
5	87	13	27	13	5	42	71	76
6	83	14	30	15	5	36	70	77

or chlorobromomethane. No correlation could be obtained between the dielectric constant of the solvent and the catalyst activity.

While the catalyst still retains a weak activity in benzenoid hydrocarbons (toluene), polymerization does not take place in saturated aliphatic hydrocarbons. Definite inhibition is also seen if the methylene chloride solution of the catalyst is diluted with pentane. This is probably the reason for the decreases in the rate of polymerization as the reaction medium becomes increasingly diluted with the polymeric olefins formed.

Finally, the influence of the molar ratio of the catalyst components should be mentioned (Table 5). If the assumptions are correct that the catalyst is a complex of both components and that this complex is in equilibrium with its components, then the activity of the catalyst mixture should increase if the concentration of the titanium component is kept constant and the molar ratio of Al:Ti rises. This is actually observed (Table 5).

Table 5. Effect of the molar ratio of CH_3TiCl_3 : CH_3AlCl_2 on conversion of ethylene and the composition of the reaction products. Ti concentration constant at 0.045 M. Further reaction conditions, see heading of Table 2. Reaction temperature: −70 °C.

Mole ratio Al : Ti	Ethylene conversion [%]	Yield of polymerized olefin [% of converted C_2H_4]					2-Ethyl-1-butene [% of C_6 fraction]	2-Ethyl-1-hexene [% of C_8 fraction]
		C_4	C_6	C_8	C_{10}	$> C_{10}$		
0.1	25	5	7	5	5	78 [*]	—	—
0.2	40	13	15	4	4	63 [*]	60	—
0.5	73	16	40	23	8	13	75	82
1.0	84	14	39	21	7	19	78	82
2.0	90	11.5	23	10	3.5	53	71	78

[*] Has vaseline-like consistency at room temperature.

In order to permit formulation of a reaction scheme for the first steps of this polymerization reaction, it was necessary to determine the constitution and the quantitative composition of the members of the homologous polymer series. Analysis by gas chromatography and infrared spectroscopy was simplified by our ability to

separate quantitatively the β-ethyl-branched α-olefins from the unbranched olefins, which are present to a small extent, using a method discovered by *Graf* [12] (see experimental section). The unbranched olefins were then investigated to determine the location of the double bond.

We regard the olefins presented in Table 6 as the primary products of the polymerization; that is, the observation that, in the unbranched C_6–C_{10} olefins, structures with an internal double bond occurs to a considerable extent is not to be considered as evidence for isomerization of α-olefins initially formed. The double bond in α-olefins is not displaced under the conditions of polymerization (– 70 °C and the presence of ethylene). The C_4 fraction consists of pure 1-butene.

From these considerations, it is possible to present a reaction scheme for the polymerization of ethylene, using the data of Table 6.

Table 6. Products of polymerization of ethylene in methylene chloride at –70 °C. Catalyst: 0.045 M Ti; 0.045 M Al. Further reaction conditions, see heading of Table 2. Ethylene conversion: 84 %.

Fraction	Yield based on ethylene conversion	Composition of fraction
C_4	14 %	100 % 1-butene no 2-butene
C_6	39 %	15 % 1-hexene 6 % 2-hexene 1 % 3-hexene 78 % 2-ethyl-1-butene
C_8	21 %	7.5 % 1-octene 1 % 2-octene 6.5 % 3-octene + 4-octene 82 % 2-ethyl-1-hexene 3 % 4-ethyl-1-hexene
C_{10}	7 %	10–12 % 1-decene (+ 4-ethyl-1-octene) 1 % 2-decene 5–8 % 3-decene + 4-decene *ca.* 1 % 5-decene *ca.* 80 % 2-ethyl-1-octene (+ 2,4-diethyl-1-hexene)
C_{12}	6 %	
C_{14}	5 %	
C_{16}	8 %	

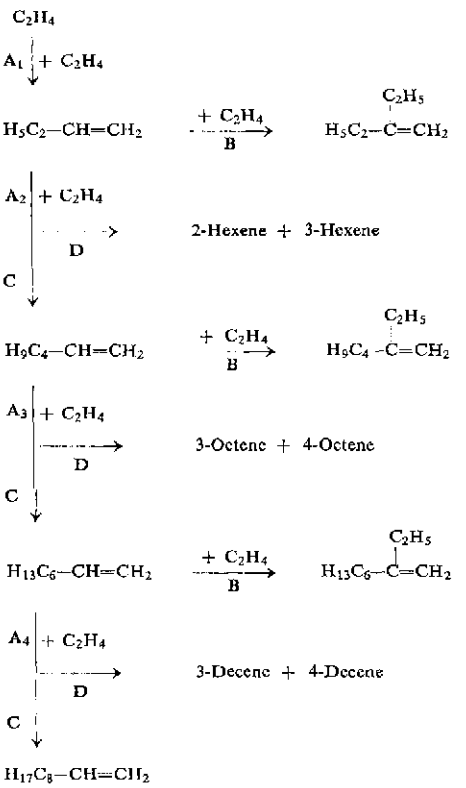
Thus, two concurrent reactions actually take place:

1. Polymerization of ethylene proceeds as a reaction (A) with straight-chain propagation. Proton or hydride ion transfer occurs during the growth steps, so that, alongside the α-olefins (reactions A, C), straight-chain olefins with the same number of carbons and internal double bonds are also formed (reactions A, D). The latter are incapable of further reaction.

2. α-Olefins formed by reaction (A) are ethylated in the β-position according to reaction (B). Thus β-ethyl-branched polymer-homologous α-olefins are formed, which take part in the further polymerization to only a slight extent. They are therefore present to an extent of about 80 % in the fractions obtained on working up the polymerization mixture (see Table 6).

[12] German Patent 1112063 (Febr. 8th, 1959), Farbwerke Hoechst AG.; German Patent Application 1130434 (March 3rd, 1959), Farbwerke Hoechst AG.

The rapid decay of the growth reaction and the high content of β-ethylated olefins denotes that the rates of reactions (A) and (B) are of about the same order of magnitude. Quantitative evaluation of Table 6 – to the extent permissible by the undetermined composition of the fractions C_{12} and above – shows that the ratio of olefins formed according to (A) and (B) is approximately unity.



Scheme 1. Course of polymerization of ethylene (deduced from Table 6)

To complete the polymerization scheme and to consider the formation and composition of these fractions, the following should be added.

1. The 2-ethyl-1-olefins, especially 2-ethyl-1-butene and 2-ethyl-1-hexene, have only limited stability under the conditions of polymerization. They dimerize slowly under the influence of the catalyst, a reaction which is even caused by the aluminum component of the catalyst alone. From Tables 2, 3, and 5, it is seen how the reaction conditions affect the formation of these dimerization products. The dimers and co-dimers of 2-ethyl-1-butene and 2-ethyl-1-hexene comprise the bulk of the C_{12}–C_{16} olefins.

2. 4-Ethyl-1-olefins are also formed in small amount along with the 2-ethyl-α-olefins. The C_8 fraction contains 3 % 4-ethyl-1-hexene. These 4-ethyl-α-olefins react further according to (A) and (B), and form difficultly identifiable portions of the higher fractions. The path by which they are produced cannot be determined. An attempt to produce 4-ethyl-1-hexene from 2-ethyl-1-butene by introduction of ethylene under the same conditions as those used during the polymerization was unsuccessful.

Copolymerization of α-Olefins and Ethylene

It could not be deduced from the results of the low-temperature polymerization of ethylene whether the straight-chain α-olefins cited in Scheme 1 are active intermediates in the growth and ethylation reactions, or

whether a reaction chain leads directly to the individual polymerized olefins.

Our experiments to settle this question yielded the surprising result that propene and 1-butene, as well as homologous α-olefins, are polymerized only very slowly at −80 °C by our Al-Ti catalyst. The catalyst solution assumes a deep red color upon addition of the olefin and thus exhibits the same coloration phenomenon as occurs when ethylene is passed in. However, there is an almost complete absence of polymerization in this case.

Rapid conversion is observed if ethylene is added to the catalyst solution containing the α-olefin at −80 °C. Ethylene reacts with the α-olefin to form liquid copolymers, which have been analyzed (Table 7). From the results obtained on conversion of several α-olefins (C_3–C_{10}), it is gathered that the reaction leads quite selectively to 2-ethyl-α-olefins.

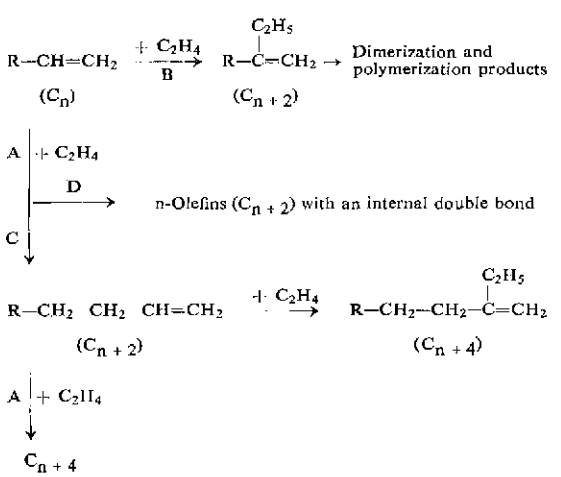
The procedure is simple, provided a cooling medium is available, and is a useful preparative method: by means of it, α-olefins are transformed by direct catalytic ethylation, in 80 % yield and with high conversion of olefin, into 2-ethyl-α-olefins which are obtained by distillation in 90–95 % purity. The sole by-product is the straight-chain olefin with the same number of carbon atoms and an internal double bond. α-Olefins with branching at C-2 or C-3 (2-ethyl-1-butene, 3-methyl-1-butene) do not react. Even a methyl group at C-4 of an olefin (4-methyl-1-pentene) has an inhibiting, effect.

Interesting deductions can be made if the results are compiled into a reaction scheme (Scheme 2). α-Olefins with even-numbers of carbon atoms (1-butene, 1-hexene, and 1-octene) fit readily into Scheme 1 for the polymerization of ethylene, whereby reactions (A) and (B) begin at the step which corresponds to the olefin

Table 7. Copolymerization of α-olefins with ethylene in methylene chloride at −80 °C. (Catalyst: CH_3TiCl_3 and CH_3AlCl_2 in molar ratio of 1 : 1; Ti concentration 0.045 M; ethylene was introduced into the solution of the α-olefin; molar ratio C_2H_4: α-olefin 1 : 1,5; duration of experiment 5 hrs.; all figures in %).

	Starting olefin, C_n							
	Propene [*]	1-Butene	1-Pentene	1-Hexene	1-Heptene	1-Octene	1-Decene	4-Methyl-1-pentene
Conversion (based on α-olefin charged)	40	61	71	75	67	80	81	54
Products (based on α-olefin used)								
Olefin $C_n + 2$	55	80	87	86.5	85	87	70	52 [**]
of which:								
n-olefin is	4.5	8.7	8.5	8	10	9	9	27
2-ethyl-α-olefin is	95.5	91.3	91.5	92	90	91	91	73
Olefin $C_n + 4$		8	5.5	8	7.5	6	5.5	5.5 [**]
of which:								
2-ethyl-α-olefin is		80	85	86	82	80	80	
Olefin $C_n + 6$		1.5	1.5	1.5	1.5	1.5	1.5	
Dimerization product of 2-ethylolefins $C_n + 2$		3	4	4	4.5	5	20	37 [**]
Polymeric products of 2-ethylolefins $C_n + 2$	40	6.5						

[*] Molar ratio of Al : Ti in catalyst = 0.5. [**] Contaminated with homopolymers of ethylene.



Scheme 2. Copolymerization of α-olefins and ethylene

used. If the results of the copolymerization experiments are compared with those of the homopolymerization, it appears that β-ethylation (B) has become the dominant reaction, and that straight chain propagation (reaction A) is strongly suppressed. The growth reaction is practically ended after only two steps.

Table 8. Ratio of olefins formed according to paths (A) and (B) of Scheme 2, calculated from Table 7

Starting olefin	Σ Olefin from (A) (n-olefin $C_n + 2$ + Σ olefin $C_n + 4$ + Σ olefin $C_n + 6$) [%]	Σ Olefin from (B) (2-Ethylolefin $C_n + 2$ + dimer + polymer) [%]	(A) : (B)
1-Butene	16.5	82.5	0.2
1-Pentene	14.4	83.6	0.17
1-Hexene	16.4	83.6	0.2
1-Heptene	17.5	81.0	0.22
1-Octene	15.4	84.1	0.18

The values shown in Table 8 indicate that, for all olefins, the ratio of polymerized olefin produced according to reactions (A) and (B) amounts to about 0.2. The charged olefin is thus consumed five times as

rapidly by ethylation at the β-carbon atom as by the chain propagation reaction, which attacks the α carbon. In the homopolymerization of ethylene, the ratio (A) : (B) was equal to unity.

The composition of the olefin fraction C_{n+2} from Table 7 is shown in Table 9. It is seen that the n-olefins with internal double bonds comprise 7–8 % of the C_{n+2} fraction. This type of olefin is the only straight-chain product of monoethylation if the normal 1-olefins, which are present only in very small amounts, are disregarded. The same type of olefin was found in the homopolymerization of ethylene in the C_6 and C_8 fractions. The abundance of olefins with Δ^3- and Δ^4-double bonds is surprising. Only in the olefins formed from propene and 1-butene (*viz.* n-pentenes and n-hexenes) does the double bond appear most frequently between C-2 and C-3. The ethylene-homologous olefins produced from 1-pentene and higher α-olefins contain practically no isomers with Δ^2-, Δ^5-, or Δ^6-double bonds (insofar as the latter are possible). Migration of the double bond can be excluded from consideration, since any starting olefin which has not reacted is recovered as α-olefin.

Table 9. Composition of the olefin fractions C_{n+2} in the copolymerization of α-olefins with ethylene (all figures in %)

Polymer olefins C_{n+2}	Starting olefin Cn						
	Propene	1-Butene	1-Pentene	1-Hexene	1-Heptene	1-Octene	1-Decene
n-1-Olefin	0.3	1.7	≤0.3	0.2	≤0.1	≤1	≤0.5
n-2-Olefin	4	6	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1
n-3-Olefin n-4-Olefin		1	8.0	7.2	8	8	*ca.* 8
n-5-Olefin						≤0.1	<0.1
n-6-Olefin							<0.2
2-Ethyl-1-olefin	95.5	91.3	91.5	92	90	91	91

The fact that the double bond is evidently fixed in a particular place during the formation reaction allows a deeper insight into the mechanism of the reaction (see below).

Reaction Mechanism

The preceding sections have shown that the mechanism of the polymerization of ethylene with the soluble two-component catalyst $RTiCl_3 \cdot RAlCl_2$ in chlorinated hydrocarbons reveals no relationship to the mechanism of the anionic polymerization of ethylene by the method of *Ziegler* [1].

The interpretation of the experimental findings in terms of a cationic mechanism, similar to the polymerization of isobutylene or α-olefins with Friedel-Crafts catalysts, also encounters difficulties, for the following reasons:

1. The rate at which the simple olefins are polymerized by a cationic mechanism decreases in the sequence

$$(CH_3)_2C{=}CH_2 > CH_3{-}CH{=}CH_2 > CH_2{=}CH_2.$$

Isobutylene itself is polymerized rapidly even below −100 °C. The polymerization of propyleen at −80 °C already requires very active catalysts ($AlBr_3$ + HBr) [13]. Low temperature polymerization of ethylene with Friedel-Crafts catalysts has not been observed previously, to our knowledge. It is known that liquid ethylene can be used as an inert solvent in the technical polymerization of isobutylene with boron trifluoride or aluminum chloride at *ca.* 100 °C [14]. Even at +10 °C and with application of pressure, the polymerization of ethylene in the presence of large amounts of aluminum chloride proceeds very slowly [15]. Results with $RTiCl_3 \cdot RAlCl_2$ as catalyst show that the olefins, in terms of their reaction rate, should be arranged in the reverse order. Ethylene is polymerized surprisingly easily, even at −100 °C, while α-olefins (propylene, 1-butene, *etc.*) are hardly changed. Furthermore, branched α-olefins of the type $R_2C{=}CH_2$, which are very sensitive toward Friedel-Crafts catalysts, are quite stable to polymerization with the Ti-Al catalyst.

2. With decrease in temperature, the polymerization of α-olefins (propylene, isobutylene) with Friedel-Crafts catalysts yields products of increasing molecular weight. In contrast, the degree of polymerization of our low-temperature ethylene polymers is very low and decreases still further as the temperature is lowered, until the product at −100 °C consists predominently of 1-butene (see Table 2).

3. The mechanism of cationic olefin polymerization with metal halides requires the presence of cocatalysts (HCl, HBr, H_2O) [16–18]. Equation (d) can be assumed as the starting reaction for the polymerization of propylene with $AlBr_3$ + HBr as catalyst.

$$CH_2{=}\underset{}{\overset{CH_3}{CH}} + HBr + AlBr_3 \rightarrow CH_3{-}\underset{\oplus}{\overset{CH_3}{CH}}\ [AlBr_4]^{\ominus} \qquad (d)$$

The chain grows by addition of propylene onto the alkyl cation.

The two-component organometallic system $RTiCl_3 \cdot RAlCl_2$ is not compatible with the presence of free protons in the reaction medium. This excludes the possibility of proton-donating cocatalysts, so that the polymerization initiated by this system must be explained by another mechanism.

One can only speculate as to the structure of the active catalyst complex since it is in equilibrium with its

[13] *C. M. Fontana* and *G. A. Kidder*, J. Amer chem. Soc. *70*, 3745 (1948); *C. M. Fontana*, *G. A. Kidder*, and *R. G. Herold*, Ind. Engng. Chem. *44*, 1688 (1952).

[14] *H. Güterbock:* Polyisobutylen. Springer. Heidelberg 1959; *H. Güterbock* in *Houben-Weyl:* Methoden der organischen Chemie. 4th Ed., Thieme, Stuttgart 1961, vol. XIV/1, p. 627.

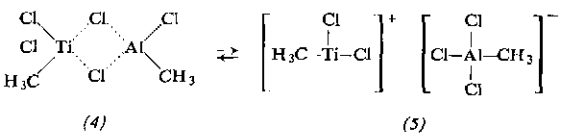
[15] *A. W. Nash* et al., J. Instn. Petroleum Technologists *16*, 830 (1930).

[16] *A. G. Evans* and *M. Polanyi*, J. chem. Soc. (London) *1947*, 252.

[17] *P. H. Plesch*, *M. Polanyi*, and *H. A. Skinner*, J. chem. Soc. (London) *1947*, 257.

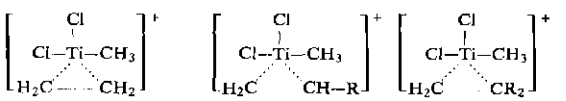
[18] *C. M. Fontana* in *P. H. Plesch:* Cationic Polymerisation and Related Complexes. W. Heffer & Sons, Cambridge 1953.

components, and this precludes its isolation. Our hypothesis is based on the concept that the complex $RTiCl_3 \cdot RAlCl_2$ exists in saturated aliphatic hydrocarbons as the inactive structure *(4)*, while in strongly polar chlorinated hydrocarbons (CH_2Cl_2, CH_3Cl), it has at least partially the ionic complex structure *(5)*.



(4) *(5)*

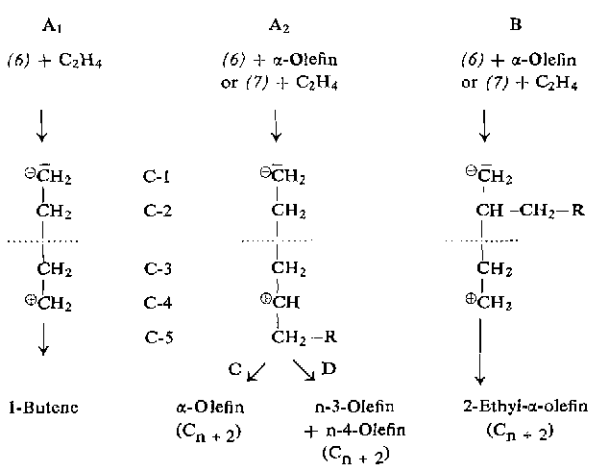
The strong deepening of color observed on addition of ethylene or an α-olefin to the catalyst solution can be interpreted as being due to the coordinate binding by the titanium cation of an olefin molecule.



(6) *(7)* *(8)*

The olefin complexes *(6)* and *(7)* react with ethylene to form short-lived intermediates, which become stabilized by intramolecular proton or hydride ion displacement, with formation of the primary products found on analysis.

The results summarized in Tables 6 and 7 and the polymerization schemes deduced from them can easily be interpreted by three dimerization steps (A_1, A_2, and B), in which only the combinations ethylene + ethylene (A_1) and ethylene + α-olefin (A_2, B), but not α-olefin + α-olefin, are possible. The dimerization step ethylene + α-olefin can be initiated by interlinking of the molecules at either the α-or the β-carbon atom of the olefin (A_2 and B, respectively).



For the stabilization of the short-lived intermediates, which are formulated as 1,4-dipoles, intramolecular prototropies (C-3 or C-5 → C-1) and hydride ion shifts (C-2 → C-4) are assumed in A_1 and A_2. In reaction A_1 (initiation reaction), both shifts lead to the α-olefin (1-butene) or to its π-complex with the titanium cation *(7)*, which reacts further with ethylene according to A_2 or B. In reaction A_2, the hydride ion shifts yield ethylene-homologous α-olefins (C_{n+2}) or their π-complexes *(7)*.

The proton shifts from C-3 or C-5 to the anionic C-1 lead to unbranched olefins (C_{n+2}) with a Δ^3- or Δ^4-double bond (see Table 9).

The intermediates formed in reaction B cannot react further by proton shifts, since these would lead to 3-methyl-α-olefins, which are not observed. The branched α-olefins which are isolated in the homopolymerization and in the β-ethylation of α-olefins are pure 2-ethyl-α-olefins, the formation of which is explainable by hydride ion shift (from C-2 to C-4).

The formation of 4-ethyl-1-hexene, which is found in small amount in the C_8-fraction of the ethylene polymer (Table 6), can be interpreted by the same mechanism if one assumes that 2-ethyl-1-butene reacts with the ethylene complex *(6)*. The 4-ethyl-α-olefins can, however also be formed by reaction of ethylene with the cationic olefin complex *(8)*.

Secondary Products of the Low-Temperature Polymerization

The primary products of ethylene polymerization are stable only below −60 °C, so that they increase in the solution and can be isolated in high yield. With increasing temperatures longer residence times, and higher catalyst concentrations, they transform with increasing rapidity into secondary products. Even at −50 °C, polymerization in methylene chloride under standard conditions yields liquid polymerized olefins, in which primary C_4, C_6, C_8, and C_{10} olefins are present only to the extent of 18 %; the remaining 82 % of the polymer are composed of branched olefins with more than ten carbon atoms (see Table 2). Figure 1 shows the composition of the polymer.

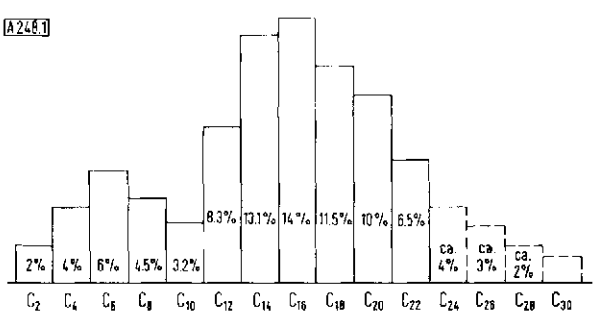


Fig. 1. Composition of an ethylene polymer (prepared at −50 °C in methylene chloride; cf. Table 2).
Abscissa: Number of carbons in the olefins produced.

The anomalous distribution of polymerized olefins, which is characterized by a second maximum at C_{14}-C_{16}, may be explained by assuming that the 2-ethyl-α-olefins with 6, 8, and 10 carbon atoms initially formed are transformed, under the conditions of polymerization, into dimeric, codimeric, and trimeric products. Model experiments with 2-ethyl-1-butene and 2-ethyl-1-hexene gave the same result: From the mixture of both ethyl-branched olefins, a mixed polymeric olefin was formed, which was separated by distillation into dimeric, codimeric, and trimeric products. These products were

compared with the olefins with the same numbers of carbon atoms from the ethylene polymerization. The analysis showed close agreement.

The 2-ethyl-α-olefin fraction with 6 and 8 carbon atoms diminishes in bulk with increasing polymerization temperature, whereas the fraction of olefins with more than 10 carbon atoms increases (see Table 2). This also indicates the formation of these olefins from 2-ethyl-α-olefins of the hexene and octene fractions. The structure of the polymerized olefins with twelve or more carbon atoms can be deduced from the mode of their formation. As expected, they contain only internal double bonds, with a neighboring branch ($\rangle$C=CH–).

Formation of Polyethylene Oils

Above −50 °C, controlled polymerization of ethylene is no longer possible. The catalyst system loses its specificity. In this temperature range, it catalyzes not only the primary reactions (see Polymerization Scheme 1) and oligomerization of the 2-ethyl-α-olefins, but also acquires an activity toward straight-chain olefins with terminal and internal double bonds. Hence, at higher temperatures, further growth of ethylene polymers results from homo- and copolymerization of a large number of olefins (including ethylene) and affords polyethylene oils, the molecular weights and structures of which are governed by the experimental conditions (see Table 10).

Table 10. Properties of some polyethylene oils as a function of reaction temperature.

Reaction conditions		Product			
Temp. [°C]	Solvent	Average Mol.Wt.	Olefin content [*]	Kinematic viscosity at 37.8 °C [centistokes]	Pour point [°C]
+20	$CHCl_3$	550	49	74.9	−17
+10	$CHCl_3$	480	57	42.2	−18
0	CH_2Cl_2	430	71	28.6	−22
−10	CH_2Cl_2	380	77	20.7	−36
−10	CH_2Cl_2	380	77	20.7	−36
−20	CH_2Cl_2	330	87	12.5	−49
−30	CH_2Cl_2	310	87	11.8	−60

[*] Calculated from hydrogenation-iodine number and molecular weight.

The fact that the olefin content, calculated from the hydrogen uptake during catalytic reduction, is too low indicates that the reactivity of the double bond in the polyethylene oils is partly lowered, so that their assay by known chemical means fails. Studies on model substances also show this.

With regard to their composition, the polyethylene oils are aliphatic, highly branched olefinic hydrocarbons. Polymerization of ethylene with aluminum chloride at 110 °C under pressure according to *Zorn* [19] affords oils consisting largely of branched paraffin chains, containing as many as four naphthene rings [20]. Here the structure of the ethylene polymer initially formed (probably produced by a cationic mechanism) is basically altered under the influence of the strong Friedel-Crafts catalyst via secondary reactions such as alkylations, dehydrogenations, isomerizations, cyclizations, and cracking processes.

The organometallic Ti–Al catalyst is capable of inducing the primary step of ethylene polymerization at a temperature which may be 100 to 200 °C lower than that of a polymerization with aluminum chloride. It is therefore possible with this catalyst to break off the polymerization at any desired stage and to protect the polymer molecules from major structural changes.

Experimental

Starting Materials

Dimethylaluminum chloride and methylaluminum dichloride were prepared from technical methylaluminum sesquichloride by treatment with sodium chloride or aluminum chloride. It was then fractionally distilled and analyzed by chlorine determination [21, 22].

Methyltitanium trichloride was prepared from titanium tetrachloride and dimethylaluminum chloride; it was more or less freed from methylaluminum chloride (Al content < 1 mole %) by grinding with sodium chloride and subsequent sublimation [23]. The product was kept at −78 °C (dry ice), and freshly weighed out under nitrogen for each catalyst solution.

Methylene chloride and chloroform (unstabilized) were obtained directly from our production plant, shaken with phosphorus pentoxide, and finally fractionated, the initial and final cuts (each 10–15 %) being discarded. The distillates were kept and withdrawn under nitrogen. The other solvents were dried by customary methods, fractionated, and also stored under nitrogen.

Ethylene, propylene, and 1-butene were available in pure form (minimum content ≥ 99.9 %; O_2 < 10 ppm; water < 50–100 ppm). Ethylene was freed from traces of water by cooling at −78 °C; propylene and 1-butene were dried over magnesium perchlorate. 1-Pentene, 1-hexene, and 1-octene were 99 % pure, 1-heptene 95 %, and 1-decene 98 % pure. The liquid olefins were dried over sodium and stored under nitrogen. The purity of the olefins were checked by gas chromatography and infrared spectroscopy.

Polymerization of Ethylene

A two-liter cylindrical stirred vessel fitted with a low-temperature thermometer and gas inlet tube was filled under extra pure nitrogen and with complete exclusion of moisture with 400 ml of dry solvent (mostly methylene chloride). The vessel stands in a benzine bath. The bath temperature was regulated by evaporation of liquid nitrogen; this gave the desired internal temperature and permitted the necessary temperature control during the polymerization to within ±1 °C. The catalyst was then added and pure, dry ethylene admitted. Unreached ethylene was vented through a mercury seal.

[19] *H. Zorn*, Angew. Chem. *60*, 185 (1948).

[20] *R. Kaufhold, G. Geiseler*, and *F. Runge*, Angew. Chem. *66*, 208 (1954).

[21] *F. C. Hall* and *A. W. Nash*, J. Instn. Petroleum Technologists *23*, 679 (1937).

[22] *A. v. Grosse* and *I. N. Mavity*, J. org. Chemistry *5*, 108 (1940).

[23] *C. Beermann* and *H. Bestian*, Angew. Chem. *71*, 618 (1959); German Patent 1023766 (Dec. 16th, 1955), Farbwerke Hoechst AG.

After the desired reaction time had elapsed, the catalyst was inactivated by addition of 25 ml of tridecyl alcohol (made from tetrapropylene) and 20 ml of phenoxypropylene oxide (for binding HCl). The mixture was fractionally distilled.

To obtain the higher fractions ($> C_{12}$) in pure form, the catalyst was inactivated with 25 ml of methanol; the mixture was then washed with water and dilute caustic soda solution to remove catalyst components. After long drying over sodium sulfate, the mixture was fractionally distilled. The low-boiling products ($< C_8$) are partly lost in this procedure. On the other hand the higher fractions (from C_{14}) recovered when following the other procedure described above, are contaminated.

Catalyst

For Tables 2 to 4: A mixture of 2.0 ml (18 millimoles) of titanium tetrachloride and 3.2 ml (36 millimoles) of methylaluminum sesquichloride, was prepared at room temperature, allowed to react for 15 min, and then diluted with 20 ml solvent (CH_2Cl_2).

For Tables 5 and 6: The required volume (1–20 ml) of 1.8 M methylaluminum dichloride solution and 10 ml of 18 M methyltitanium trichloride solution were added successively to a volume of precooled methylene chloride so as to give a total volume of 400 ml.

Copolymerization of α-Olefins with Ethylene

A one-liter reaction vessel equipped with a thermometer and a gas inlet tube was charged with 200 ml of methylene chloride and *ca.* 220 ml of dry, oxygen-free α-olefin and cooled by evaporating liquid nitrogen to an internal temperature of −80 °C; 10 ml of 1 M methylaluminum dichloride solution and 10 ml of 1 M methyltitanium trichloride solution were added as catalyst. Sufficient dry ethylene was immediately admitted to provide a molar ratio of ethylene: α-olefin of 1:1 to 1.5:1. After reaction for five hours at − 80 °C, the catalyst was inactivated as described for ethylene above, and the mixture worked up.

Preparation of Polyethylene Oils

A 3.5-liter reaction vessel fitted with a gas inlet tube, a thermometer, and a dropping funnel was charged under nitrogen with 1400 ml of dry, stabilizer-free chloroform (or methylene chloride). The latter was then agitated and saturated with pure, dry ethylene. The catalyst solution [5.5 ml (50 mmole) of titanium tetrachloride + 9.0 ml (100 mmole) of methylaluminum sesquichloride diluted to 500 ml] was added dropwise, the admission of ethylene being continued, so that an ethylene consumption of about 120 g/hr was achieved. The temperature was maintained at the desired level by cooling with isopropanol/dry ice. After 5 to 9 hours, the reaction was stopped with 50 ml of isopropanol, the solution washed with water until neutral, and dried, the solvent being then distilled off. To remove the low-boiling fractions, a fraction was distilled off over a small column up to 75 °C/15 mm Hg. The residue consisted of colorless to clear yellow oils having the properties described in Table 10.

Analysis

The 2-ethyl-1-olefins produced as main products react quantitatively and rapidly with chlorosulfonyl isocyanate [24] (see below for procedure), while olefins which are not branched at the double bond do not give this reaction. In this manner, the principal components of the C_6 to C_{10} fractions could be determined quantitatively and separated. The reaction products in the C_6 and C_8 fraction were converted into crystalline derivatives in good yields [2-(anilinosulfonamino)-2-ethyl-1-butanecarbon anilide, m.p. 141 2 °C, or 6-ethyl-6-*n*-butyldihydrouracil, m.p. 119–20 °C] and identified by mixed melting points with the corresponding derivatives prepared from 2-ethyl-1-butene or 2-ethyl-1-hexene.

Quantitative Separation of 2-Ethyl-1-olefins

The olefin mixture (25 ml) was weighed into a 100-ml flask provided with devices to ensure exclusion of moisture, cooling (20 °C), and magnetic stirring, and treated with a small excess of chlorosulfonyl isocyanate [25]. Stirring was continued for *ca.* 30 min, and the bath temperature was then slowly raised to +40 °C. Finally, the volatile portions (unreacted olefins and excess reagent) were carefully distilled off *in vacuo* (0.1 mm Hg) into a trap cooled to −78 °C (bath temperature up to 40 °C). Unreacted olefin can be isolated for further analysis from the contents of the trap by careful treatment with ice water. The content od 2-ethyl-1-olefin in the sample was determined (±1 % for contents above 30 %) from the weight of adduct remaining in the flask (distillation residue).

Because of the susceptibility of the adducts to decomposition above +40 °C, this method is suitable only for olefins with up to 8 carbon atoms. By using fluorosulfonyl isocyanate, one obtains addition products that are stable to +70 °C, so that olefins containing up to 12 carbon atoms can thus be assayed.

In order to elucidate the nature of the side reactions which occur during low-temperature polymerization, quantitative analysis of the by-products is important (Tables 8 and 9). This was achieved after separation of the main components up to the C_8 fraction by a combination of gas chromatography and infrared spectroscopy. In the higher fractions, the location of the double bond was also determined by ozonolysis.

Samples (0.5 to 1 ml) of fractions with a uniform number of carbon atoms, freed from the main components, were ozonized in pentane at −78 °C, and the products were converted with Raney nickel [26] into carbonyl compounds, which were then identified by gas chromatography with the aid of reference compounds.

Received, May 16th, 1962 [A 248/67 IE]

[24] Cf. *R. Graf*, Liebigs Ann. Chem. in the press; German Patent 1112063 (Febr. 28th, 1959) Farbwerke Hoechst AG.

[25] *R. Graf*, Chem. Ber. *89*, 1071 (1956).

[26] *N. C. Cook* and *F. C. Whitmore*, J. Amer. chem. Soc. *63*, 3540 (1941).

Tri-[*o*-(diethylaminomethyl)phenyl]chromium

By Prof. Dr. G. Bähr[*] and Dipl.-Chem. H. Zohm

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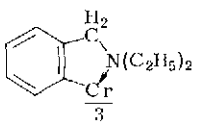
The results of earlier work on the synthesis of organometallic chelate compounds of aluminium [1] and beryllium [2] can also be applied to transition metals. By using the sequence of reactions:

o-toluidine → *o*-bromotoluene → *o*-bromobenzyl bromide → *o*-bromobenzyldiethylamine → *o*-lithiobenzyldiethylamine,

and by treating the latter with dry chromium(III) chloride in ether at room temperature under nitrogen, we obtained the organochromium chelate *(1)*.



(1)

The reaction proceeds smoothly; after about 15 minutes, the stoichiometric quantity of chromium(III) chloride is used up and only traces remain. Compound *(1)* forms lustrous garnet-red crystals, which are soluble in ether, tetrahydrofuran, and benzene, which are purified by recrystallisation from hot isooctane, and which exist as single molecules in benzene. As expected, *(1)* is extremely sensitive towards atmospheric oxygen (the finely divided material smoulders), is hydrolysed by water to chromium(III) oxyhydrate and benzyldiethylamine, but remains unaltered under dry nitrogen[3].

Further investigations using extensive variations of the transition metal and organic ligands are in progress.

Publication withheld until now at the request of the authors.
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[*] New address: Eduard-Zintl-Institut, Technische Hochschule, Darmstadt (Germany).

[1] *G. Bähr* and *G. E. Müller*, Chem. Ber. *88*, 251, 1765 (1955).

[2] *G. Bähr* and *K.-H. Thiele*, Chem. Ber. *90*, 1578 (1957).

[3] The chelate *(1)* is paramagnetic and non-conducting in nitrobenzene.

1,3,5-Triethynylbenzene

By Dr. W. Hübel and Dipl.-Chem. R. Merényi

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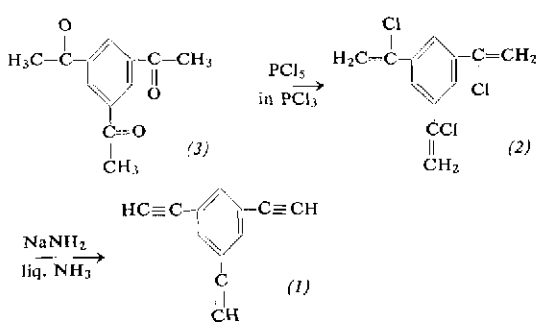
Both 1,3,5- and 1,2,4-triethynylbenzene were obtained for the first time by removal of the trimethylsilyl groups from the corresponding tris-(trimethylsilylethynyl)-tris-(trimethylsilyl)benzene with KNH_2 in liquid ammonia [1]. 1,3,5-Triethynylbenzene *(1)* was found to be readily accessible also by the synthetic route *(3)* → *(1)*.



Chlorination of the keto groups in 1,3,5-triacetylbenzene [2] was effected successfully by stirring it for 16 hours with the calculated quantity of PCl_5 in PCl_3 as solvent at 40 °C. The PCl_3 and the $POCl_3$ formed were removed by distillation *in vacuo*, and the residue was hydrolyzed and subjected to chromatography in benzene on acidic Al_2O_3. Benzene acted as eluent for 1,3,5-tris-(α-chlorovinyl)benzene *(2)*, which was obtained in 65 % yield as a yellow oil. Compound *(2)* was crystallized from ethanol as colorless needles, m.p. 36–38 °C, which sublime *in vacuo* above 30 °C and which turn gradually yellow in air.

Compound *(2)* was not attacked by boiling methanolic caustic potash but was transformed into stable 1,3,5-triethynylbenzene *(1)* in 60 % yield by treatment with $NaNH_2$ in liquid ammonia. Compound *(1)* crystallized from ethanol in thin needles, m.p. 105–107 °C, which sublime at 50–60 °C.

Received, September 21st, 1962 [Z 350/209 IE]

[1] *W. Hübel* and *R. Merényi*, Chem. Ber., in the press.

[2] Org. Synth. *27*, 91 (1947); cf. *B. Paulis*, Ph. D. thesis, University of Amsterdam, 1956.

Peptide Synthesis from Esters Using Imidazole Catalysis

Peptide Syntheses, XXVI [*]

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The use of alkyl esters of amino acids as acylating agents in peptide synthesis [1] has been neglected because of their relative slowness to react. Imidazole is a strong catalyst for the hydrolysis of phenyl esters, particularly when electron-attracting groups are present in the aromatic ring [2,3], but only acts as well in this way on alkyl esters when these are derived from strong acids [4,5].

Following an observation by *W. Löwe* of the readily occurring imidazolysis of α-hydroxylactones we have investigated the effect of imidazole on the aminolysis of the methyl ester of carbobenzoxy-DL-alanine (I) by glycine derivatives and have found that, on heating the components together for 3–4 hours in imidazole at 80 °C, good yields of peptides were obtained.

Stirring of I with finely powdered Na glycinate, which is difficultly soluble in imidazole, and working up gave 62 % carbobenzoxy-alanylglycine (II). By using the tetraethylammonium salt of glycine which is readily soluble in imidazole, 74 % II was obtained; with the t-butyl ester of glycine (the alkyl residue of which is not aminolysed), a yield of 78 % of the t-butyl ester of II was produced. The questions of racemization in these simple peptide syntheses and their application to longer and more complicated peptides are now being investigated.

Received, October 9th, 1962 [Z 364/215 IE]

[*] Communication No. 25: *T. Wieland* and *R. Sarges*, Liebigs Ann. Chem. *658*, 181 (1962).

[1] See, *e.g.*, the review by *T. Wieland*, Angew. Chem. *63*, 7 (1951).

[2] *M. L. Bender* and *B. W. Turnquest*, J. Amer. chem. Soc. *79*, 1652, 1658 (1957).

[3] *T. C. Bruice* and *G. L. Schmir*, J. Amer. chem. Soc. *79*, 1663 (1957).

[4] *D. M. Brauwer*, *M. J. van der Vlugt*, and *E. Havinga*, Kon. Akad. Wetenschap. Proc., Ser. B *60*, 275 (1957).

[5] *W. P. Jencks* and *J. Carriulo*, J. Amer. chem. Soc. *83*, 1743 (1962).

NAD Analogues with a Substituted Purine Moiety

By Prof. Dr. G. Pfleiderer, Dr. C. Woenckhaus, and Dipl.-Chem. K. Scholz

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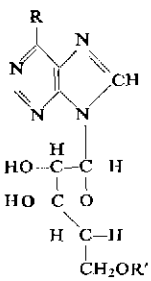
For some time we have been investigating the influence of the purine moiety of nicotinamide adenine dinucleotide (NAD) [1] and have hence synthetized various NAD analogues: nicotinamide thiopurine dinucleotide (NTD) [2], nicotinamide methylthiopurine dinucleotide (NMTD), and nicotinamide purine dinucleotide (NPD). 6-mercapto purine riboside *(1)* was employed as starting material. Phosphorylation was achieved after prior introduction of an isopropylidene group into the 2,3-position of the ribose according to the method of *Roy* et al. [3]. 6-Methylmercapto-9-(β-D-2,3-isopropylidene ribofuranosyl)purine was obtained quantitatively by methylation of the isopropylidene derivative of *(1)* with CH_3I. Nebularine-5'-phosphate *(2)* was produced in 40 % yield by desulfurization with Raney nickel of 6-methyl mercapto-9-(β-D-ribofuranosyl)purine-5'-phosphate *(3)*. The condensations with nicotinamide mononucleotide were carried out in aqueous pyridine with dicyclohexylcarbodiimide [4]. Purification of the NAD analogues was effected on columns of the formate form of Dowex-1 by gradient elution with increasing concentrations of formic acid. Following this treatment, impurities could no longer be detected by chromatography or electrophoresis (yields 10 to 15 %).

NTD is yellow; in its difference spectrum (NTD to reduced NTD), maxima appear at 340 and 318 mμ. The preparation is 85 % pure. The molar ratios of ribose and phosphoric acid are 1:1. Its Michaelis constant is 6.6×10^{-4} M, measured with alcohol dehydrogenase from yeast, being therefore three times greater than that of NAD. NMTD is pale yellow and has two maxima in its difference spectrum, *viz.* at 295 and 340 mμ.



	R	R'
(1)	SH	H
(2)	H	PO_3H_2
(3)	SCH_3	PO_3H_2

NPD is colorless. Its spectrum resembles that of NAD, with an absorption maximum at 263.5 mμ at pH 9.5. At this wavelength, $\varepsilon_{NPD} = 12.6\times10^3$ and $\varepsilon_{red.NPD} = 9.0\times10^3$. Ribose:phosphate = 1:1. The Michaelis constant, measured with yeast alcohol dehydrogenase, is, as for NAD, 2.4×10^{-4} M.

Received, October 19th, 1962 [Z 384/207 IE]

[1] *G. Pfleiderer, E. Sann,* and *F. Ortanderl,* Biochem. biophysica Acta, in the press.

[2] *M. R. Atkinson, J. F. Hackson, R. K. Morton,* and *A. R. Murray,* Nature (London) *196*, 35 (1962).

[3] *J. K. Roy, D. C. Kvam, J. L. Dahl,* and *R. E. Parks,* J. biol. Chemistry *236*, 1158 (1961).

[4] *N. A. Hughes, G. W. Kenner,* and *A. Todd,* J. chem. Soc. (London) *1957*, 3733.

Synthesis of an Internucleotide Bond Using Picryl Chloride

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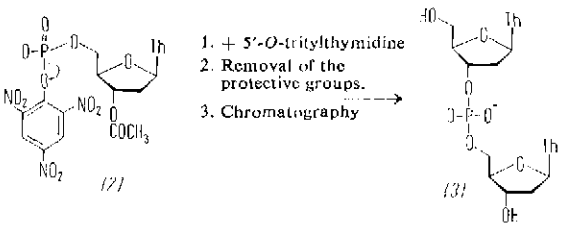
Picryl chloride *(1)* is suitable for phosphorylation reactions [1]. We have now employed *(1)* to form an internucleotide bond. In the presence of pyridine/acetonitrile, 5'-AMP reacts with *(1)* and methanol to give the methyl ester of 5'-AMP in 84 % yield. 3'-*O*-acetyl-5'-thymidylic acid reacts with picryl chloride to give the unisolated intermediate product *(2)*, which reacts with 5'-*O*-tritylthymidine (molar ratio nucleotide to nucleoside 1:1) to yield the dinucleoside phosphate *(3)* [2], after removal of the protective groups.



The reaction is carried out in pyridine/acetonitrile.

With a 2.5-fold excess of *(1)*, 64 % of compound *(3)* is formed in 24 hours at room temperature (chromatographic separation of the reaction products, spectrophotometric estimation); after 45 hrs. the reaction is 76 % complete. No by-products are observed in the chromatogram after working-up.

Received, October 24th, 1962 [Z 378/210 IE]

[1] *R. Wittmann,* Lecture, Chemiedozenten-Tagung, Munich 1961; Chem. Ber., in the press.

[2] *T. M. Jacob* and *H. G. Khorana,* Chem. and Ind. *1962*, 932.

Quaternization of Triphenylphosphine

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A publication [1] about the reaction of trimethylphosphine with NO leads us to publish some investigations on triphenylphosphine. On treating triphenylphosphine *(1)* with NOCl in ether at low temperatures under exclusion of air and moisture, compound *(2)* was obtained quantitatively; no quaternary salt could be obtained even at −50 °C. The additional products obtained were nitrogen and NCl_3, which was identified by its behaviour on distillation and by its reaction with NH_4OH. The reaction of *(1)* with NOCl therefore proceeds according to the equation:

$$\underset{(1)}{3\,(C_6H_5)_3P} + 3\,NOCl \rightarrow \underset{(2)}{3\,(C_6H_5)_3PO} + N_2 + NCl_3$$

Quaternization of *(1)* occurs on reaction with tosylates. Lower alkyl tosylates and benzyl tosylate are especially suitable. n-Octyl tosylate favors the oxidation of *(1)* rather than its quaternization.

$$(C_6H_5)_3P : R\cdot O\text{-}Ts \rightarrow (C_6H_5)_3\overset{\oplus}{P}\text{—}R\ \ \overset{\ominus}{TsO}$$

Table 1. Triphenylalkylphosphonium tosylates $(C_6H_5)_3\overset{\oplus}{P}$—R $\overset{\ominus}{Ts}$—O

R	m.p. [°C]	Yield [%]
CH_3	139.5—140.5	80
C_2H_5	93—94	87
n-C_4H_9	140.5—142	44
C_6H_5—CH_2	172.5—173.5	92

The phosphonium tosylates can undergo a normal Wittig-reaction; *e.g.* benzylidene-cyclohexane is obtained in good yield from benzyltriphenylphosphonium tosylate and cyclohexanone [2].

Received, October 25th, 1962 [Z 390/217 IE]

[1] *M. Halmann* and *L. Kugel,* J. chem. Soc. (London) *1962*, 3272.

[2] *G. Wittig* and *W. Haag,* Chem. Ber. *88*, 1654 (1955).

Cyclopentadienylcycloheptatrienylchromium(0)

By Prof. Dr. E. O. Fischer and Dipl.-Chem. S. Breitschaft

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The yellow-green, paramagnetic (one unpaired electron) cyclopentadienylcycloheptatrienylchromium(I) cation, $[C_5H_5CrC_7H_7]^+$, was prepared in 75 % yield by brief treatment of cyclopentadienylbenzenechromium(I), $C_5H_5CrC_6H_6$ [1], with cyclohepta-1,3,5-triene under nitrogen in the presence of $AlCl_3$, followed by hydrolysis. The complex ion is closely analogous to $[Cr(C_6H_6)_2]^+$ and is quite stable in water. It can be precipitated as its hexafluorophosphate (μ_{eff} = 2.0 Bohr magnetons), perchlorate, or reineckate. It can be reduced with alkaline $Na_2S_2O_4$ solution to give uncharged cyclopentadienylcycloheptatrienylchromium(0), $C_5H_5CrC_7H_7$, which gives deep blue solutions in organic media and is very sensitive to air. The blue-green compound can be sublimed *in vacuo* at 80 °C, melts at approximately 230 °C, dissolves in its monomeric form in benzene, and is diamagnetic. According to its nuclear magnetic resonance spectrum in C_6D_6, it has only two types of protons, in a ratio of 5:7 with τ-values of 6.90 and 5.08, respectively, *i.e.* this is a genuine penetration complex isoelectronic with $Cr(C_6H_6)_2$ and having two highly symmetrized rings. Its infrared spectrum shows characteristic bands which can be assigned unequivocally, *viz.* at 1423, 1110, 1014/1004, 822, (808) cm^{-1} for the π-bonded five-membered ring, and at 1244, 970, 863, (808) cm^{-1} for the seven-membered ring. The very similar absorptions [2] of the paramagnetic $C_5H_5VC_7H_7$ (one unpaired electron) prepared previously [3], which lie at 1421, 1108, 1012/1003, 802, (784) cm^{-1} and 1240, 957, 851, (784) cm^{-1} respectively, confirm that it has an identical structure and that the vanadium compound also has its molecule built up in a highly symmetrical manner. The dipole moment of $C_5H_5CrC_7H_7$ is 0.79 ± 0.05 Debye in benzene and 0.73 ± 0.05 Debye in cyclohexane; this proves that there is a slight charge separation in the complex. Such separation is probably to be interpreted for the time being in the sense of a δ^+-charge on the seven-membered ring and a δ^--charge on the five-membered ring. We assume the rings to be situated parallel to and opposite to each other.

Received, November 2nd, 1962 [Z 383/206 IE]

[1] *E. O. Fischer* and *H. P. Kögler*, Z. Naturforschg. *13b*, 197 (1958).

[2] *H. P. Fritz*, Habilitationsschrift, Universität München 1962.

[3] *R. B. King* and *F. G. A. Stone*, J. Amer. chem. Soc. *81*, 5263 (1959).

Thermochromy and Photochromy of Dehydrodianthrones

By Prof. Dr. G. Kortüm and Dr. G. Bayer

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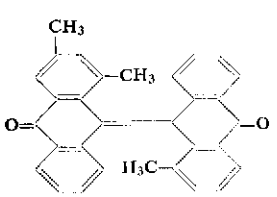
der Universität Tübingen (Germany)

It was established spectroscopically that, after irradiation of the photo-chemically stable compound 1,3,6′,8′-tetramethyldehydrodianthrone *(1)* [1], two further forms of the molecule, B and C, are found at low temperatures in addition to the form A which is stable at room temperature.



(1)

The differences in their spectra are as follows:

Form A has the first absorption maximum at 26000 cm^{-1} (log ε = 4.18; A-band).

Form B at 15000 cm^{-1} (log ε = 4.3; B-band). Its ultraviolet spectrum is only slightly different from that of the A-form.

Form C has two smaller maxima at 21000 and 22500 cm^{-1} (C-bands) and the rest of its ultraviolet spectrum is completely different from that of the A-form; a further C-band occurs for instance at 31000 cm^{-1}.

Since it is impossible to prepare the pure B or C form, extinction coefficients can be given only approximately.

When the sulfuric acid adduct of *(1)* [2] is hydrolyzed in 10 % aqueous alcohol at −90 °C, exclusively B-form is produced in addition to the A-form; this enabled the above assignment of the bands to be made. The height of the B-band is here greater by a factor of approximately twenty-five than those observed with thermochromy of unsubstituted dehydrodianthrone [1].

The molecular forms B and C are reconverted into the A-form above certain temperatures which lie, depending on the nature of the solvent, between −80 and −50 °C. In the reconversion, the rate constant $k_{B\rightarrow A}$ is greater than $k_{C\rightarrow A}$ by a factor of 2 to 5.

After irradiation at low temperatures, the quantitative proportion of the three forms to one another depends on external conditions. For instance, with pyridine or ethyl acetate as solvent, the C-bands are much higher than the B-band. On the other hand, in triacetine, which solidifies to a glass at −50 °C, the B-band is very high and the C-bands are only recognizable as a broadening of the remaining A-hand; the relationships are similar when isopentane is used as solvent. It is quite possible that also in the thermochromy of dehydrodianthrone two chromophoric constituents are formed. This may provide an explanation of the contradictions [1, 3, 4] regarding the paramagnetism of the thermochromic and photochromic forms of this compound.

An investigation of the possibilities of isolation of the different forms is in progress; this will be described in detail shortly in the Zeitschrift für Elektrochemie.

Received, November 5th, 1962 [Z 385/211 IE]

[1] *G. Kortüm*, Angew. Chem. *70*, 14 (1958); further references are given here.

[2] *G. Kortüm, W. Theilacker, H. Elliehausen*, and *H. Zeininger*, Chem. Ber. *86*, 294 (1953).

[3] *W. G. Nielsen* and *G. K. Fraenkel*, J. chem. Physics *21*, 1619 (1953).

[4] *E. Wassermann*, J. Amer. chem. Soc. *81*, 5006 (1959).

Purification and Properties of Oxynitrilase from Bitter Almonds

By Wolfgang Becker [1], Dr. U. Benthin [2], Dr. E. Eschenhof [3], and Prof. Dr. E. Pfeil

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Oxynitrilase, one of the components of the emulsin complex, effects the formation of optically active mandelonitrile from benzaldehyde and hydrocyanic acid. The enzyme is extracted with dilute ammonia (pH 7 7.5) from expressed residues obtained during almond oil recovery (*Placenta amygdalarum amarum*). Associated protein is removed *via* an isoelectric precipitation series (7 steps). The crude enzyme preparation, which can be preserved in the dry state, is precipitated by ethanol (75 %).

Further purification occurs by adsorption on ECTEOLA-cellulose and elution with pyridine acetate buffer at pH 4.9. The active fractions are desalted on a sephadex column, other impurities being removed at the same time. Solutions of pure oxynitrilase are obtained. After freeze-drying, they are found

to be uniform in the ultracentrifuge [4], the Tiselius electrophoresis apparatus, and in immunological tests.

The enzyme is a yellow chromoproteid (λ_{max} = 457 and 389 mμ); its coenzyme is flavine adenine dinucleotide. Coenzyme and apoenzyme are separated by treatment with HCl/ammonium sulfate. Neither fraction can effect oxynitrile synthesis on its own. However, they recombine in weakly alkaline medium to reform the active enzyme.

Received, November 5th, 1962 [Z 387/212 IE]

[1] Diploma thesis, Universität Marburg, 1962.

[2] Ph. D. thesis, Universität Marburg, 1959.

[3] Ph. D. thesis, Universität Marburg, 1962.

[4] We wish to thank Prof. Dr. *Schultze* and his colleagues Dr. *Mahling*, Dr. *Störiko*, and Dr. *Schwick* (Behring-Werke, Marburg) for purity controls.

Formation of 2,3-Dehydroquinoline as an Intermediate

By Doz. Dr. T. Kauffmann and cand. chem. K. Udluft

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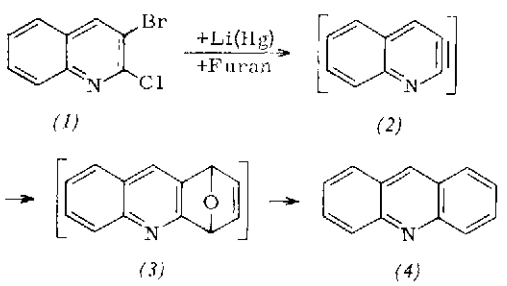
der Technischen Hochschule Darmstadt (Germany)

Whereas other attempts to detect the 2,3-dehydroquinoline as a reaction intermediate have had negative results [1], application of the method of *Wittig* and *Pohmer* [2] for the detection of arynes to 2-chloro-3-bromoquinoline *(1)* [3] was successful: after shaking a solution of the base *(1)* in furan with lithium amalgam at room temperature for 5 days, a small quantity of acridine *(4)* was obtained, which, by analogy with the formation of isoquinoline [4] and phenanthridine [1] from 4-chloro-3-bromopyridine and 4-chloro-3-bromoquinoline, respectively, may be formed *via* the intermediates 2,3-dehydroquinoline *(2)* [5] and 1,4-dihydroacridine-1,4-epoxide *(3)*.



(1) *(2)* *(3)* *(4)*

The acridine was identified unequivocally by two-dimensional paper and thin-layer chromatography and by similar chromatography of the decomposition products resulting from irradiation, and was isolated in 0.1 % yield in the form of its chloro-aurate (not quite pure) after enrichment by column chromatography. When, instead of *(1)*, 2,3-dichloroquinoline was treated with lithium amalgam and furan, no acridine could be detected in the reaction mixture.

Received, November 12th, 1962 [Z 388/213 IE]

[1] *T. Kauffmann, F.-P. Boettcher*, and *J. Hansen*, Liebigs Ann. Chem. *659*, 102 (1962).

[2] *G. Wittig* and *L. Pohmer*, Chem. Ber. *89*, 1334 (1956).

[3] *C. Kaneko*, Chem. pharmac. Bull. (Tokyo) *7*, 276 (1959).

[4] *T. Kauffmann* and *F.-P. Boettcher*, Chem. Ber. *95*, 949 (1962).

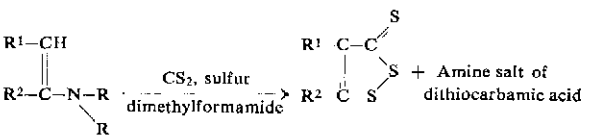
[5] *R. J. Martens* and *H. J. den Hertog*, Tetrahedron Letters (London) *1962*, 643, were recently able to detect (using gas chromatography) the formation of quinoline on treatment of 2-chloro-3-bromopyridine with lithium amalgam in furan, and thus to demonstrate the intermediate occurrence of 2,3-dehydropyridine.

Synthesis of Trithiones by Simultaneous Reaction of Carbon Disulfide and Sulfur with Enamines [1]

By Dipl.-Chem. J. Fabian, Dr. K. Gewald, and Prof. Dr. R. Mayer

Institut für Organische Chemie der Technischen Universität Dresden (Germany)

4,5-Disubstituted trithiones (1,2-dithiole-3-thiones) are formed in good yield by an exothermic reaction at room temperature of enamines with carbon disulfide and sulfur in polar solvents, such as dimethylformamide:



(1) $R^1/R^2 = -(CH_2)_3-$; *(2)* $R^1/R^2 = -(CH_2)_4-$

Thus, 1-morpholinocyclopent-1-ene forms 4,5-trimethylenetrithione *(1)* in 50 % yield, m.p. 123 °C, and 1-morpholinocyclohex-1-ene gives 45 % of 4,5-tetramethylenetrithione *(2)*, m.p. 101–102 °C (from ethanol).

(1) and *(2)* are identical with authentic specimens prepared by a different route [2]. The present synthesis is based on an electrophilic attack of the carbon disulfide and a simultaneous nucleophilic influence of the sulfur which is incorporated. It is very versatile, and is being intensively studied by us at present.

Received, November 12th, 1962 [Z 401/224 IE]

[1] Communication No. XIV on Schwefel-Heterocyclen (Heterocyclic Sulfur Compounds). Communication No. XIII: *K. Gewald*, Z. Chem., in the press.

[2] German Patent 909097 (Feb. 28th, 1951), inventors: *A. Lüttringhaus* and *U. Schmidt*; Chem. Zbl. *1954*, 10104; *U. Schmidt*, Diploma thesis, Universität Freiburg/Brsg., 1951; *U. Schmidt, A. Lüttringhaus*, and *H. Trefzger*, Liebigs Ann. Chem. *631*, 129 (1960); *M. Fröde*, Diploma thesis Technische Universität Dresden, 1961; *E. Hoffmann*, Diploma thesis Technische Universität Dresden, not yet complete.

Catalysis of H-D Exchange in Cyclooctatetraene by Cycloocta-1,3,5-triene

By Dr. G. Schröder

Union Carbide European Research Associates, Brussels (Belgium)

The vinyl acidity of the hydrogens of cyclooctatetraene *(1)* is so small that H-D exchange in the system C_8H_8/ROK/ROD is not observed.

Exchange cannot be effected by means of higher temperatures, since dimerization of *(1)* becomes a side- or even the main reaction. Thus, a mixture of *(1)* and alkoxide/alcohol at 140 °C gives cycloocta-1.3.5-triene in yields of up to 30 %, together with a brown polymeric powder [1]. A dimer of *(1)*, tricyclo[8,4,2,$0^{2,9}$]hexadeca-3,5,7,11,13,15-hexaene *(2)*, described by *Jones* [2], reduces *(1)* to cycloocta-1,3,5-triene under the catalytic effect of alkoxide.

We have found that H-D exchange in *(1)* is catalysed by cycloocta-1,3,5-triene in a basic medium [3].

On heating a solution of 100 μl of *(1)* (purified *via* its $AgNO_3$ complex), 10 μl of cycloocta-1,3,5-triene, and 10 % (based on the alcohol) of $(n\text{-}C_3H_7)_3COK$ in 5 cm^3 of $(n\text{-}C_3H_7)_3COD$ for 64 hrs. in an ampoule in a bath of boiling methanol, the *(1)* recovered [4] shows an extremely strong C-D absorption band at 2225 cm^{-1} in its infrared spectrum. Practically [5] no incorporation of deuterium is observed with pure *(1)* under the same reaction conditions without added cycloocta-1,3,5-triene. The experimental results may be explained in the

following manner. In the system ROK/ROD, cycloocta-1,3,5-triene is deuterated *via* a series of equilibrium reactions. The base ROK forms a deuterated cyclooctatetraenyl dianion from the deuterated cycloocta-1,3,5-triene. In an equilibrium described recently by *Katz* [6], this deuterated dianion transfers two electrons to the *(1)* present in the solution. Deuterated *(1)* is obtained by way of the anion radical stage from the deuterated dianion, and non-deuterated dianion is obtained from non-deuterated *(1)*, whereby the latter is again reconverted into deuterated dianion in the system ROK/ROD.

Received, November 13th, 1962 [Z 403/227 IE]

[1] Base-catalysed isomerization of *(1)* in di-β-methoxyethyl ether, on the other hand, gives benzocyclobutene in *ca.* 44% yield, among others products. *G. Eglinton, R. A. Raphael* and *R. G. Willis*, Proc. chem. Soc. (London) *1962*, 334.

[2] *W. O. Jones*, Chem. and Ind. *1955*, 16.

[3] Compound *(2)* is even more suitable as a catalyst than cycloocta-1,3,5-triene.

[4] Compound *(1)* was separated from the reaction mixture by distillation (oil pump vacuum: 0.1 mm), passed through a condenser (0 °C), and condensed in a cold trap (−75 °C). Contamination of the product by alcohol was 2% at the most, judging by gas chromatography.

[5] Under these conditions, formation of traces of *(2)* cannot be avoided.

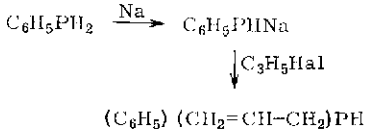
[6] *T. J. Katz*, J. Amer. chem. Soc. *82*, 3784 (1960).

Phenylallylphosphine

By Dr. E. Steininger and Dr. M. Sander

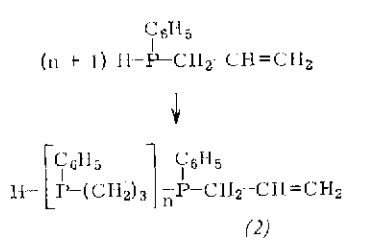
Battelle-Institut, Frankfurt/Main (Germany)

For the first time, the preparation of an unsaturated secondary phosphine has been accomplished. Monosodium phenylphosphide was prepared by a known procedure [1] starting from phenylphosphine and sodium in ether, and then treated with allyl chloride or bromide.



(1)

The phenylallylphosphine formed could not at first be isolated. It was only when the solvent was removed *in vacuo* directly after the preparation of *(1)*, that it was obtained by distillation in a good vacuum in 45–50% yield ($n_D^{20} = 1.5734$, b.p. 57 °C/0.1 mm. On storage, the phosphine gradually polymerizes, even at 0 °C, to give *(2)*:



(2)

This polyaddition proceeds rapidly on heating or in light of short wavelength, hence *(2)* always appears as a by-product when *(1)* is distilled.

Received, November 14th, 1962 [Z 391/218 IE]

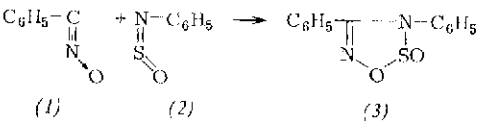
[1] *F. Pass, E. Steininger*, and *H. Schindlbauer*, Mh. Chem. *90*, 792 (1959).

4,5-Diphenyl-1,2,3,5-thiaoxadiazole-1-oxide

By Dr. P. Rajagopalan and Dr. H. U. Daeniker

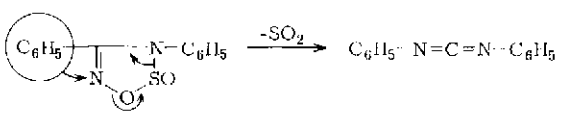
Forschungslaboratorium, Pharmazeutische Abteilung der CIBA AG., Basel (Switzerland)

Benzonitrile oxide *(1)* reacts exothermically with sulfinylaniline *(2)* in ether to give a colorless crystalline adduct $C_{13}H_{10}N_2O_2S$ (m.p. 72–73 °C) in good yield. On the basis of the well-known 1,3-addition reactions of benzonitrile oxide [1], the chemical behaviour of sulfinylaniline [2–4], and the infrared spectrum of the product (presence of a strong peak at 1198 cm^{-1}, corresponding to a cyclic sulfite grouping [5]; absence of absorption at 1080 cm^{-1} typical of a sulfinamide function [2]), structure *(3)* is likely to be the correct one. Additional proof is provided by the results of thermal decomposition.



(1) *(2)* *(3)*

When heated to 100 °C, the product *(3)* is cleaved almost quantitatively into sulfur dioxide and *N,N'*-diphenylcarbodiimide *(4)*, a pale yellow oil, $C_{13}H_{10}N_2$, b.p. 96–98 °C/0.08 mm. The formation of *(4)* from *(3)* presupposes the occurrence of a phenyl-migration, for which the following mechanism is suggested:



(3) *(4)*

Received, November 15th, 1962 [Z 393/219 IE]

[1] *A. Quilico* and *G. S. D'Alcontres*, Gazz. chim. Ital. *80*, 140 (1950), and subsequent papers; *R. Huisgen* et al., Tetrahedron Letters *1961*, 583, 1587.

[2] *G. Kresze* et al., Angew. Chem. internat. Edit. *1*, 89 (1962).

[3] *O. Wichterle* and *J. Roček*, Chem. Listy *47*, 1768 (1953).

[4] *R. Huisgen* et al., Liebigs Ann. Chem. *658*, 169 (1962).

[5] *P. B. D. de la Mare* et al., J. chem. Soc. (London) *1956*, 1813.

Tris(trialkoxysilyl)amines and Related Compounds

By Prof. Dr. U. Wannagat and Dr. H. Bürger

Institut für Anorganische Chemie der Technischen Hochschule Graz (Austria)

Metal derivatives of alkoxydisilazanes and organo-alkoxydisilazanes such as $[(RO)_3Si]_2NH$, $[R'(RO)_2Si]_2NH$, or $[R''R'(RO)Si]_2NH$ [1] can be prepared in benzene solution or directly with $NaNH_2$. Benzine is added to facilitate crystallization of the sodium bis(organo/alkoxysilyl)amides [2]. $NaN[Si(OCH_3)_3]_2$, m.p. 182–184 °C; $NaN[Si(O\text{-}i\text{-}C_3H_7)_3]_2$, m.p. 204–206 °C; $NaN[Si(CH_3)(OCH_3)_2]_2$, m.p. 171–172 °C; $NaN[Si(O\text{-}i\text{-}C_3H_7)(CH_3)(C_2H_3)]_2$, m.p. 70 °C; and others were prepared in this way. In organic solvents, even nonpolar solvents, they are moderately to very soluble, exist as dimers, and react with $SiCl_4$ or $RSiCl_3$, but not with R_3SiCl or $(RO)_3SiCl$, to give triply silyl-substituted amines such as $[(CH_3O)_3Si]_2NSiCl_3$, b. p. 100 °C/1 mm Hg; $[(CH_3)(OCH_3)_2Si]_2NSi(CH_3)Cl_2$, b. p. 79 °C/2 mm Hg; or $[(CH_3)(C_2H_3)(O\text{-}i\text{-}C_3H_7)Si]_2NSi(CH_3)(C_2H_3)Cl$, b. p. 110 °C/1 mm Hg. From these, symmetric and asymmetric triply trialkoxysilyl- and organo/alkoxysilyl-substituted amines can be prepared by alcoholysis in the presence of

pyridine, or by reaction with alkali alkoxide: *e. g.* $[(CH_3O)_3Si]_3N$, b.p. 110 °C/3 mm Hg; $[(CH_3)(CH_3O)_2Si]_3N$, b.p. 90 °C/4 mm Hg; or $[(CH_3)(C_2H_3)(i\text{-}C_3H_7O)Si]_3N$, b.p. 108 °C/1 mm Hg. On account of the complete shielding effect of isopropyl groups, $[(i\text{-}C_3H_7O)_3Si]_3N$, m.p. 267 °C, b.p. 284 °C, which is almost spherical, is distinguished by its surprising resistance to hydrolysis.

Received, November 19th, 1962 [Z 402/226 IE]

[1] *H. Bürger* and *U. Wannagat*, Z. anorg. allg. Chem., in the press.

[2] Cf. *U. Wannagat* and *H. Niederprüm*, Chem. Ber. *94*, 1540 (1961).

Silylamino-Substituted Grignard Reagents

By Prof. Dr. U. Wannagat and Dr. H. Kuckertz

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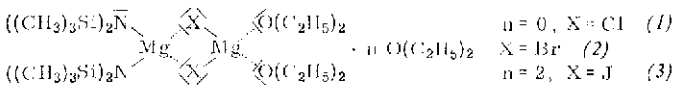
Reaction of Grignard compounds with hexamethyldisilazane leads to silylaminomagnesium halide derivatives, which crystallize exceptionally well when their concentrated solutions in ether are strongly cooled. Their analyses, molecular

$$[(H_3C)_3Si]_2NH + RMgX \rightarrow RH + [(H_3C)_3Si]_2NMgX$$

weights, properties, and reactions indicate binuclear complexes linked by halogen bridges, *viz.* di-μ-halogeno-tetrakis-(trimethylsilyl)diaminodimagnesium bis(diethyl etherate) or tetra(diethyl etherate):



$n = 0$, X = Cl *(1)*
X = Br *(2)*
$n = 2$, X = J *(3)*

The bromo derivative, which presumably is initially present as *(2)*·$2O(C_2H_5)_2$, dissolves on thawing in the ether of crystallisation and, once this has vaporized, turns into finely divided, crystalline *(2)*. The somewhat indefinite melting points are 106 °C for *(1)*, 98 °C for *(2)*, and 60 °C for *(3)*. At higher temperatures, elimination of ether is accompanied by pyrolysis to form volatile SiN-derivatives.

Compounds *(1)*–*(3)* are easily soluble in gasoline, cyclohexane, benzene, and toluene, and very readily in ether. They are rapidly decomposed by water. A precipitate having the approximate composititon

$$[((CH_3)_3Si)_2N]_2Mg \cdot 2MgI_2 \cdot 2O(C_2H_5)_2$$

is obtained when a solution in benzene of *(3)* is refluxed for a fairly long time. *(3)* is decomposed by dioxan into $MgI_2 \cdot 2OC_4H_8O$ and $Mg[N(Si(CH_3)_3)_2]_2 \cdot 3OC_4H_8O$, the latter being a white, crystalline, very hygroscopic solid, which is very readily soluble in organic solvents. Treatment of *(3)* with $NaN[Si(CH_3)_3]_2$ leads to predominantly NaI and $Mg[N(Si(CH_3)_3)_2]_2 \cdot O(C_2H_5)_2$, which on sublimation at 100 °C/1 mm changes into a Magnesium tetrakis(trimethylsilyl)diamide which is free from ether. In boiling benzene, *(2)* no longer reacts with $SiCl_4$ like the alkali bis(silyl)amides to yield triply silyl-substituted amines.

Received, November 19th, 1962 [Z 395/225 IE]

Perchloropropa-1,2-diene, a Highly Reactive Allene

By Prof. Dr. A. Roedig, Dr. G. Märkl, and Dipl.-Chem. B. Heinrich

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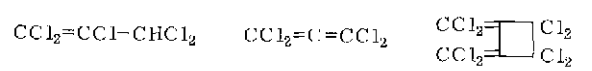
Dehydrochlorination of 3*H*-pentachloroprop-1-ene *(1)* with KOH in boiling toluene, or preferably, with $NaNH_2$ in liquid ammonia [1] yields a cyclic compound *(3)* of m.p 93 °C [2,3].

The intermediate occurrence of *(2)* has now been demonstrated by its synthesis. If the dehydrohalogenation is performed according to a procedure described in [1], *viz.* at −75 °C in liquid ammonia diluted with propane, the reaction occurs



(1) *(2)* *(3)*

mainly at the propane-ammonia interface, and the formation of *(3)* can be completely suppressed in favor of *(2)*. On evaporating off the propane *in vacuo* at −75 °C, perchloropropa-1,2-diene *(2)* is obtained quantitatively as an almost colorless powder. It may be stored unchanged almost indefinitely at this temperature; on removal of the cooling, however, a strongly exothermic reaction sets in rapidly, the material liquefies, boils, and dimerizes to almost pure *(3)*. At −30 °C, this reaction goes to completion within about 90 minutes. At −50 °C, the infrared spectrum of *(2)* is very simple and shows a peak at 5.09 μ, characteristic of allenes. The purity of *(2)* was proved further by chlorination at low temperatures, which yielded exclusively perchloropropene (b.p. 93–94 °C/11 mm; $n_D^{20} = 1.5480$). At low temperatures, *(2)* reacts with cyclopentadiene without undergoing dimerization to *(3)*. The composition of the product $C_8H_6Cl_4$ (m.p. 43.5–45 °C) obtained corresponds to that of the expected diene-adduct.

The reactivity of *(2)* exceeds by many times that of all known allenes. This unusual activity contrasts with the known deactivating and stabilizing effects usually exerted on carbon-carbon double bonds by perchloro-substitution.

Received, November 19th, 1962 [Z 394/220 IE]

[1] *F. Bischoff*, Diploma Thesis, Universität Würzburg, 1954.

[2] *A. Roedig* and *F. Bischoff*, Naturwissenschaften *49*, 448(1962).

[3] *J. Brandmüller*, *E. Ziegler*, and *A. Roedig*, Naturwissenschaften *49*, 466 (1962).

Note added in proof: According to *K. Pilgram* and *F. Korte*, Tetrahedron Letters *1962*. 883, compound *(2)* can also be obtained by dehydrochlorinating *(1)* in the gas phase. The product, however, is less pure.

A Neutral Complex of Aluminum with 2,2′-Bipyridyl

By Prof. Dr. S. Herzog, Dipl.-Chem. K. Geisler [1], and Dipl.-Chem. H. Präkel [2]

Institut für Anorganische Chemie der Universität Greifswald (Germany)

We have succeeded in preparing tris-2,2′-bipyridylaluminum for the first time and in two different ways. (In all operations strict exclusion of air and water is essential.)

Method a) (with *K. Geisler*): Anhydrous $AlCl_3$ (0.9 g) was dissolved in 30 ml of tetrahydrofuran and treated with 3.16 g of 2,2′-bipyridyl (molecular ratio 1:3); the suspension of the resulting white adduct was treated for reduction with three equivalents of bipyridyldilithium in tetrahydrofuran [3]. A very deep brown solution was formed, from which green crystals separated; these were recrystallized from benzene. Their analysis indicated the formula $AlDipy_3$. Yield: 1.65 g (purified). On admission of air, oxidation ensues, causing glowing and elimination of bipyridyl vapor. The compound gives yellow-brown solutions in tetrahydrofuran, benzene, or dioxan; these are instantaneously oxidized on admission of air, with lightening of color. Anaerobic decomposition occurs with alcohol and water. Anaerobic iodination in tetrahydrofuran leads to the Al(III) oxidation level with consumption of 2.97 (theory requires 3) gram-atoms of iodine. Magnetic measurement at room temperature showed the gram-sus-

ceptibility to be $\chi = 4.23 \cdot x\ 10^{-6}$ [cm³/g], which corresponds to 2.32 Bohr magnetons [4].

Method b) (with *H. Präkel*): 2,2'-Bipyridyl (0.7 g.) and 0.3 g of lithium aluminum hydride are covered with 40 ml of a mixture of benzene and tetrahydrofuran (3:1 by volume). Vigorous evolution of hydrogen begins immediately; the solution becomes red-brown, and glittering green crystals of $AlDipy_3$ separate out. After boiling the reaction mixture for two hours under reflux, the product is filtered off and extracted with benzene; yield *ca.* 0.1 g. It sublimes with partial decomposition by heating to 285 °C *in vacuo* (*ca.* 10^{-4} mm Hg). We also often observed formation of $AlDipy_3$ on treatment of bipyridyl complexes of various metals with $LiAlH_4$.

Received, November 20th, 1962 [Z 397/221 IE]

[1] Part of the diploma thesis of *K. Geisler*, Universität Greifswald, 1960.

[2] Part of Ph. D. thesis of *H. Präkel*, Universität Greifswald, not yet complete.

[3] *S. Herzog* et al., Z. Chem. *2*, 208, 225 (1962).

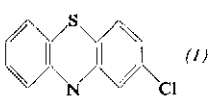
[4] We thank *W. Kalies* for carrying out the magnetic measurement.

CONFERENCE REPORTS

Action Mechanisms and Metabolism of Psychoactive Drugs Derived from Phenothiazine and Structurally Related Compounds

September 7th and 8th 1962, Paris (France)

Most of the investigations concern chlorpromazine *(1)*, the first compound of the series of psychoactive phenothiazine derivatives, and the one that is still chiefly used today.



(1)

$CH_2-CH_2-CH_2-N(CH_3)_2$

Decomposition of this compound in the human and animal organism begins simultaneously at different positions in the molecule, so that a large number of metabolic products can be found in the urine. Oxidation of the sulfur proceeds to the sulfoxide stage but never to the sulfone stage. The dimethylamino group is demethylated in stages. Both benzene rings become hydroxylated. In man, the free phenols are never found but are always esterified either with glucuronic or sulfuric acid. Generally, mainly monoglucuronides together with much less diglucuronides are found. In the urine, about 60% of the metabolites are glucuronic esters, 25% are ether-soluble.

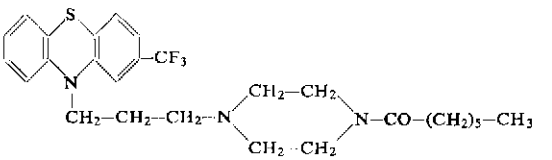
Under the influence of ultraviolet light, the metabolism of the phenothiazines is notably different from that in the organism. Free radicals split off and can be recognised in the ESR spectrum (*L. H. Piette, G. Bulow, I. S. Forster*, Palo Alto, California, U.S.A.; *C. Lagercrantz*, Göteborg, Sweden). The free radicals appear only under aerobic conditions.

In *in vitro* experiments, distinct inhibition of respiration of rat brain slices in the presence of glucose, pyruvate, or gluconate, but not of succinate as substrate when using a 0.2 millimolar concentration of chlorpromazine, was shown by *J. H. Quastel* (Montreal, Canada). Respiration stimulated with potassium ion or electrical activation was also markedly more strongly inhibited. In contrast to respiratory inhibition by barbiturate, the inhibition under *Quastel*'s conditions increased during incubation. A concentration of the medicament which markedly inhibited respiration did not noticeably affect the conversion of glucose into glutamine. Since the strongest inhibition follows stimulation of respiration by K^+, it must be concluded that the action affects primarily the nerve cell membranes. Under the experimental conditions given, imipramine reacts in the same way as chlorpromazine. In the discussion, the fact that these two medicaments have completely different modes of action was forwarded as a significant argument against the mechanism assumed by *Quastel* to be important for the action of the drug.

Investigations using radioactively labelled phenothiazine derivatives by *E. J. Van Loon* (Philadelphia, U.S.A.) showed that these medicaments are removed extraordinarily rapidly from the blood stream by the liver. The concentration in the blood of the portal vein lay about 2 to 3 times as high as that in the blood of the veins leading from the liver.

Light-adapted frogs (*Rana pipiens*) and flatfishes (*Lophosetta maculata*) were shown to exhibit darkening of the epidermis under the influence of chlorpromazine and other phenothiazines. The most active preparations were fluphenazine and trifluphenazine. All the derivatives investigated with a piperazine ring in the side chain and those with a dimethylamino group were active. Mepazine, which has a piperidine ring in the side chain, was the only inactive one. Imipramine also produced darkening in fish. All of the monoamineoxidase inhibitors tested caused lightening in the color of dark adapted animals (*G. F. Scott*, Oberlin, Ohio, U.S.A.).

S. M. Hess (New Brunswick, New Jersey, U.S.A.) described an extraordinarily slow-acting derivative. Fluphenazine enanthate *(2)*, which was injected in sesame oil solution, caused sedation lasting for over 4 weeks in experimental animals. In the dog, the antiemetic action after a single dose remained for 50 days, so that throughout that time, injection of apomorphine did not induce vomiting. In humans, too, the antipsychotic effect of a single injection lasted for 2 weeks. The drug passes extremely slowly from the blood into the brain. The amounts of the medicament or its metabolic products excreted in the urine were too small to be detected.



(2)

H. S. Posner (Washington, U.S.A.) examined the pharmacological properties of the compounds formed in the organism from chlorpromazine and promazine. The sulfoxides were invariably inactive. Removal of a methyl group was without noteworthy influence on the activity. With the *N*-oxide, also considered to be a metaholic product, a change in the character of the action was observed. In the promazine group, the 2- or 4-hydroxy derivatives were almost as active as the starting material, whereas the 1-hydroxy compound had a distinctly weaker effect.

The enrichment of phenothiazines in parts of the eye was dealt with by *J. Rutschmann* (Basel, Switzerland). Considerable deposition in the iris, retina, and choroid was found only in pigmented animals, not in albinos. The enrichment was surprisingly greatest with chlorpromazine, although, in contrast to the other phenothiazines investigated, retinopathy had never been observed with this compound.

T. Berti (Padua, Italy) reported on variations in the catabolism of phenothiazines according to species, sex, and temperature. In guinea pigs, mainly phenols were formed, in humans, sulfoxides predominated. Female rats metabolised the phenothiazines significantly more slowly than the males. In all cases, chlorpromazine caused sedation at temperatures of 13–18 °C, while stimulation occurred at 33–38 °C.

In animal experiments, the direction of exchange of materials between blood and brain was affected by phenothiazines in the same way as in all other historical and classical methods of treatment of schizophrenia (*G. Quadbeck*, Homburg/Saar, Germany).

Besides the topics quoted, clinical and microbiological problems and those of pathological anatomy were dealt with.

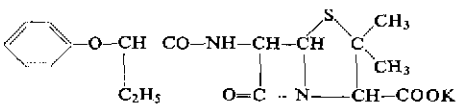
[VB 640/61 IE]

Therapy Congress and Pharmaceutical Exhibition

Karlsruhe (Germany), August 26th to September 1st, 1962

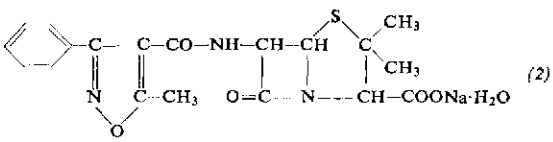
About 230 firms participated in the exhibition of pharmaceuticals. From the abundance of new preparations on display, here only a few which contain new chemical compounds can be mentioned.

New penicillin derivatives for oral administration were brought out chiefly by Farbenfabriken Bayer and Farbwerke Hoechst. Baycillin® *(1)* from Bayer resembles penicillin-V in its biological spectrum but has a greater resistance to penicillinase, so that at the Baycillin concentrations clinically attainable, staphylococci of slight to medium resistance can be inhibited. The generic name of *(1)* is propicillin; chemical name: potassium DL-α-phenoxy-n-propylpenicillanate; it is obtained by treating 6-aminopenicillanic acid with DL-α-phenoxybutyryl chloride; m.p. 210 °C (decomp.), $[\alpha]_D^{22} = +211°$ (c:3.5 in water); readily soluble in water.



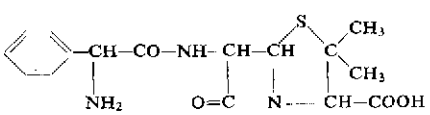
(1)

Stapenor® *(2)*, also from Bayer, differs from the classical penicillins chiefly in its high resistance to staphylococcal penicillinase and hence in its action on all penicillin-resistant staphylococci. The generic name of *(2)* is oxacillin; chemical name: sodium 5-methyl-3-phenyl-4-isoxazolyl-6-aminopenicillanate; analogous to the preparation of *(1)*, it is obtained from penicillanic acid and 5-methyl-3-phenylisoxazol-4-carbonyl chloride; m.p. 188 ° (decomp.); colorless; $[\alpha]_D^{20} = +201°$ (c:1 in water); readily soluble in water and in polar organic solvents.



(2)

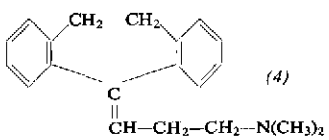
Cryptocillin®, marketed by Farbwerke Hoechst, is a penicillin derivative which corresponds to Stapenor in its synthesis and action.



(3)

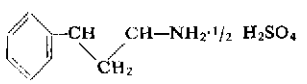
Another penicillin derivative (commercially available from Nov. 1st, 1962) is Binotal® *(3)*, the first and hitherto only derivative of 6-aminopenicillanic acid with a biological spectrum covering both Gram-negative and Gram-positive organisms. Generic name: ampicillin, chemical name: D-(−)-α-aminobenzyl-penicillin *(3)*; m.p. 207 °C (decomp.); $[\alpha]_D^{21} = +281°$ (c:1 in water); obtained by acylating 6-aminopenicillanic acid with α-phenylglycine. It contains a free amino and a free carboxyl group and has the properties of a peptide; it is soluble only in water.

A new antidepressant, amitriptylin (generic name), is marketed under the names Laroxyl® by Roche and Saroten® by Tropon-Werke. It is 5-(3-dimethylaminopropylidene)-dibenzo[a,d][1,4]cycloheptadiene hydrochloride *(4)*, a colourless crystalline substance, m.p. 196–197 °C. Similar in structure to the phenothiazines, it has a thymoleptic component as well as the properties of a tranquillizer.



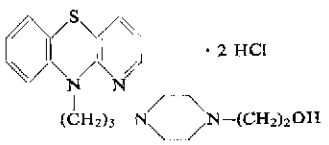
(4)

A new psychotherapeutic drug is Jatrosom® from Röhm and Haas. Besides the known Jatroneural® (a neuroleptic phenothiazine derivative) it contains the antidepressant tranylcypramine *(5)*, which has been in use for a long time in the U.S.A., Canada, and Britain. Jatrosom now brings *(5)* also onto the German market. *trans*-2-Phenylcyclopropylamine sulfate *(5)* is a powerful monoamine oxidase inhibitor, and, unlike most other MAO inhibitors, it contains no hydrazine group.



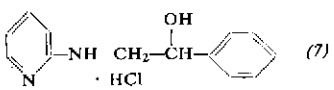
(5)

To the large number of phenothiazine derivatives known came another, 10-[3′-(1″-β-hydroxyethyl-4″-piperazinyl)propyl]-10*H*-pyrido[3,2-b][1,4]benzothiazine dihydrochloride *(6)*. Contained in the new anti-emetic Pervetral® from Homburg, it is a white, crystalline powder, soluble in water, m.p. 222 °C.



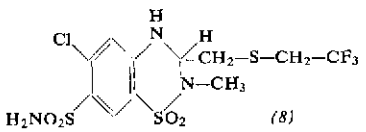
(6)

An analgesic muscle relaxant was introduced by Kali-chemie under the trademark Cabral® *(7)*; its generic name is phenyramidol hydrochloride; chemical name: 2-(β-hydroxy-β-phenylethylamino)pyridine, m.p. 138–140 °C. It is obtained by treating 2-aminopyridine with styrene epoxide in liquid ammonia in the presence of sodamide. It effects relaxation of muscle by selectively blocking certain pathways in the brainstem and polysynaptic reflexes of the spinal cord. It has a great analgetic effect on muscle pains.



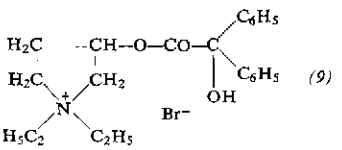
(7)

Drenusil® *(8)* from Pfizer is a new diuretic of the benzothiazine series. It ought to be a salt-removing diuretic of highest possible therapeutic safety. Drenusil effects increased removal of sodium and chloride ions in approximately equivalent amounts and causes hypokalaemia only in rare cases.



(8)

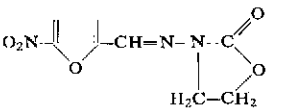
Minelsin *(9)* from Parke-Davis is a highly active anticholinergic, suitable for the treatment of various ulcers and functional disorders of the gastro-intestinal tract. It is



(9)

1,1-diethyl-3-hydroxypyrrolidinium bromide (as the benzylic ester), a white crystalline, readily water-soluble compound with an intensely bitter taste.

Furoxon from C. F. Boehringer, Mannheim, is a new chemotherapeutic agent of the nitrofuran group. Generic name: furazolidone; chemical name: *N*-(5-nitro-2-furfuryl-idene)amino-2-oxazolidone *(10)*, yellowish, light-sensitive crystals, m.p. 255 °C.



(10)

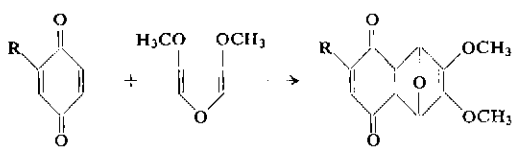
It is suitable for the treatment of infectious intestinal diseases.

[VB 652/62 IE]

Abnormal Diels-Alder Reactions between Furans and Quinones

C. H. Eugster, Zurich (Switzerland)

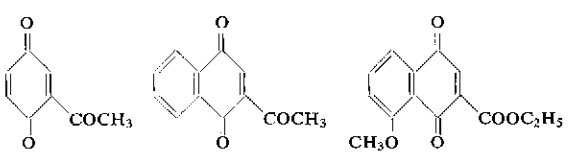
So far, it has not been possible to condense quinones with furan in the Diels-Alder reaction. Interaction occurs readily, however, with 3,4-dimethoxyfuran *(1)*, which is activated, yielding enediol-ethers of type *(2)* [1].



(1) *(2)*

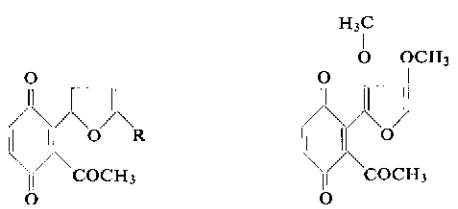
R = H; m.p. 90—91 °C
R = CH_3; m.p. 80 °C

Reaction proceeds differently with negatively substituted quinones, *e.g. (3)*, *(4)*, and *(5)*.



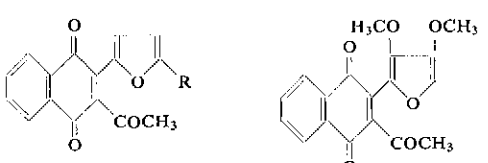
(3) [2] *(4)* [3] *(5)* [4] m.p. 102—103 °C

On condensation with furans, these yield *o*-furyl-quinones or hydroquinones, respectively *(6–12)*:



(6) R = H, m.p. 123—124 °C
R = CH_3, m.p. 121—122.5 °C
R = $CH_2CO_2C_2H_5$, m.p. 84—87 °C

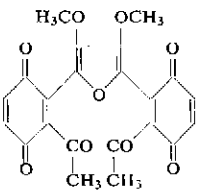
(7) m.p. 87 °C



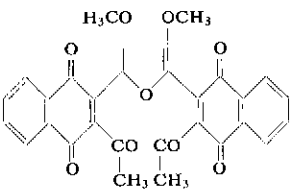
(8) R = H, m.p. 123—124 °C
R = CH_3, m.p. 129—130 °C

(9) m.p. 140—142 °C
Hydroquinone:
m.p. 120—122 °C

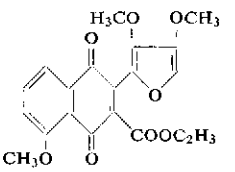
[1] *C. H. Eugster* and *A. Hofmann*, Chimia *15*, 518 (1961).
[2] *C. H. Eugster* and *P. Bosshard*, Chimia *15*, 528 (1961).
[3] *C. H. Eugster* and *P. Bosshard*, Chimia *16*, 45 (1961).
[4] *C. H. Eugster* and *R. Good*, Chimia *16*, 343 (1962).



(10) Quinone: no m.p.
Hydroquinone: m.p. 193.5–194 °C



(11) m.p. 201—204 °C



(12) m.p. 165 °C

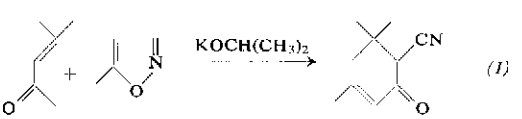
A number of reactions involving *(6)*, R=H, were described [5]. These affect the furyl residue, with participation of the *ortho*-carbonyl group.

[Max-Planck-Institut für Kohlenforschung
Mülheim/Ruhr (Germany). September 19th, 1962]
[VB 649b/58 IE]

Condensation Reactions with Isoxazoles

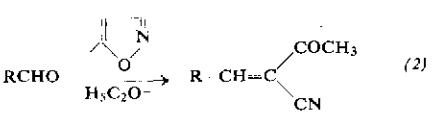
C. H. Eugster, Zurich (Switzerland)

In Michael additions on to α,β-unsaturated ketones, 5-methyl isoxazole may be employed instead of monomeric cyanacetone, which is difficult to handle. The products of the reaction are substituted β-ketonitriles of type *(1)*.



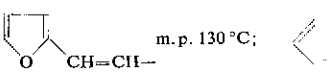
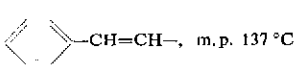
(1)

Iodomethylates of Mannich bases may also be used. Condensations involving aldehydes yield a new class of compounds, *viz.* alkylidene cyanoacetones *(2)*.



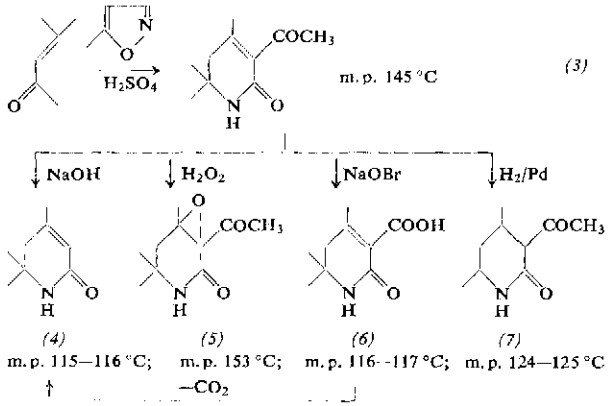
(2)

R = $(CH_3)_2CH$–, m.p. 47 °C; , m.p. 65 °C; , m.p. 83 °C;

 , m.p. 130 °C;  , m.p. 137 °C

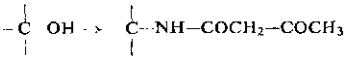
[5] *C. H. Eugster* and *P. Bosshard*, Chimia *15*, 530 (1961).

Under acidic conditions, 5-methylisoxazole and α,β-unsaturated ketones condense to yield 3-acetyl-5,6-dihydropyridones of type *(3)*.



In the same way, 5-phenylisoxazole yields 3-benzoyldihydropyridones. Thus, 3-acyl-lactams have now become easily accessible on a preparative scale.

β-Hydroxy- or β-halogeno-ketones may also serve in place of the α,β - unsaturated ketones. Propargyl carbinols (>C(OH)CH_2C≡C–) yield, after addition of $HgSO_4/H_2O$ to the reaction mixture, the same 3-acyldihydropyridones. Tertiary carbinols produce substituted acetoacetamides:



This new reaction constitutes an extension of the Ritter-Graf synthesis; however, on account of the bifunctional character of the acetoacetamido residue, it is more versatile than this reaction.

[Max-Planck-Institut für Kohlenforschung
Mülheim/Ruhr (Germany), September 19th, 1962]

[VB 649a/57 IE]

SELECTED ABSTRACTS

The preparation of vinyl chloride using fused salts as a catalyst, is reported by *W. Sundermeyer* et al. 1,1-Dichloroethane vapor is passed through a vigorously stirred melt of $ZnCl_2$/KCl heated to 330 °C. The conversion is 77%, with a yield of 97% vinyl chloride. At 260 °C, the conversion is 53% and the yield 89%. About 5% by weight of $HgCl_2$ were added to the melt in order to avoid formation of small amounts of volatile material (probably chloro-acetylene and acetylene). Vinyl chloride can also be obtained from 1,2-dichloroethane: at 260 °C, the conversion is 33.2% and the yield 76%; at 380 °C, the figures are 74.5% and 85%, respectively. Passing acetylene and HCl through a $ZnCl_2$/KCl melt containing 5% by weight of $HgCl_2$ at 250 °C gave a conversion of 70% and a yield of 89% vinyl chloride. By combining the two methods, vinyl chloride can be obtained from 1,1-dichloroethylene and acetylene (1:1) in an overall yield of 68.5% (calculated on converted dichloroethane, the yields is 137%). / Chem. Ber. *95*, 1829 (1962) / –Hg. [Rd 313/100 IE]

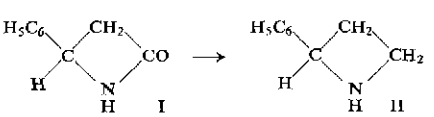
Silicon-32 has been prepared by *D. Geithoff*, using the nuclear reaction $^{32}Si(T,p)^{32}Si$. The reaction is exothermic (Q = 7.42 MeV) and its threshold energy is 3.25 MeV. For generating tritons, the reaction $^{6}Li(n,T)^{4}He$ was used. On acount of the small range of the tritons, the target material and the triton source were combined in one chemical compound. Lithium silicide, Li_2Si, was irradiated for 24 days in a reactor at a neutron flux of 1.9×10^{13} neutrons per cm^2 per sec. Seven months after termination of the irradiation (^{31}Si had decayed meanwhile), the specimen was heated with CaF_2 and H_2SO_4, SiF_4 was distilled off, and the Si was precipitated with NH_3 as silicic acid. Repetition of this procedure yielded a pure product which was ignited to give SiO_2, the activity of which was measured. ^{32}Si is a β-emitter and is therefore easily identified by its daughter isotope ^{32}P. The half-life is 650 days./ Radiochim. Acta *1*, 3 (1962) / –Ko. [Rd 362/112 IE]

Thin-layer chromatography on poly-amide layers has been used by *K.T. Wang* for the separation of phenols, phenolic carboxylic acids, and tropolone derivatives. The layers were made by applying 35 ml of a solution of 60 g of poly-ε-caprolactam in 300 ml of 80% formic acid to glass plates (18×25 cm) and drying overnight at 30 °C. The remaining formic acid was then removed by heating at 100 °C for 20 min. The finished plates bore a coating 0.055 cm thick of poly(caprolactam). Solvents particularly suitable for chromatography of phenols were ethyl acetate, chloroform, and benzene, together with cyclohexane and n-hexane. For phenolic carboxylic acids, ethyl acetate/acetic acid (95/5) was the most suitable, while tropolone derivatives were developed with cyclohexane containing acetic acid. / J. Chinese chem. Soc., Ser. II, *8*, 241 (1961) / –Ko. [Rd 360/107 IE]

In applying allyl and propargyl halides in Grignard reactions, *M. Gaudemar* uses Zn instead of Mg. Electrolytic zinc turnings plus the alkyl bromide in tetrahydrofuran provide a Grignard solution which reacts readily and without side-reactions with carbonyl compounds and nitriles. Wurtz reactions and disproportionations either do not occur at all or only to slight extents. / Bull. Soc. Chim. France *1962*, 974 / –Bs. [Rd 312/99 IE]

The crystal structure of rhenium beryllide $ReBe_{22}$ has been investigated, using X-ray analysis, by *D. E. Sands, Q. C. Johnson, A. Zalkin, O. H. Krikorian*, and *K. L. Kromholtz*. In order to prepare single-crystals, a mixture of Re and Be powders (Be in excess) was heated at 1650 °C in a BeO crucible in an atmosphere of argon. Single crystals were then picked out after comminution of the cooled specimen. $ReBe_{22}$ crystallizes in the face-centred cubic system, space group $Fd3m-O_h^7$, a = 11.561 Å, 8 formula units per unit cell. The Re atom has 16 neighboring Be atoms at distances of 2.50 to 2.53 Å. There are four classes of Be atoms: Be_1 has 2 neighboring Re atoms at 2.50 Å and 12 neighboring Be atoms at 2.46 Å, Be_2 and Be_3 each have 12 neighboring Be atoms at between 2.05 and 2.29 Å, and Be_4 has 1 neighboring Re atom at 2.53 Å and 11 neighboring Be atoms at 2.13–2.46 Å. / Acta crystallogr. *15*, 832 (1962) / –Ko. [Rd 361/113 IE]

2-Phenylazetidine and its *N*-derivatives have been synthetized by *E. Testa, L. Fontanella* and *V. Aresi* for pharmacological investigation. Reduction with $LiAlH_4$ of 2-phenylazetidin-4-one (I), obtained in 23% yield from ethyl β-amino-β-phenylpropionate and CH_3MgI, gave 2-phenylazetidine (II) in 61% yield, with 3-amino-3-phenylpropanol as a by-product (5%). Compound II, $C_9H_{11}N$, b.p. 76 78 °C/2.5 mm, is a base with pK 9.5 and can be acylated with acid anhydrides. The *N*-acyl derivatives can be reduced readily by $LiAlH_4$ to give *N*-alkyl-2-phenylazetidines without ring opening. *N*-Alkyl derivatives may also be obtained by treatment of a solution in benzene of II with alkyl chlorides in the presence of $(C_2H_5)_3N$. When dissolved in hydrochloric acid and treated



with NaOCN, II readily forms 2-phenyl-1-carbamoylazetidine. II and formaldehyde-$NaHSO_3$ give the corresponding Na 1-methanesulfonate. Its reaction with phenyl isocyanate yields 2-phenyl-1-phenylcarbamoylazetidine. On the whole, II and its derivatives are somewhat less stable chemically than 3-mono- or 3,3-disubstituted azetidines. / Liebigs Ann. Chem. *656*, 114 (1962) / –Ma. [Rd 358/108 IE]

Methoden der enzymatischen Analyse (Methods of Enzymatic Analysis [*]) Edited by *H. U. Bergmeyer*. Verlag Chemie, Weinheim/Bergstrasse 1962. 1st Edition, xxii + 1065 pp. 78 illustrations, 41 tables, 4 plates, linen-bound, price DM 99.-- (about $25.00).

The praiseworthy task of collecting together practicable methods of enzymatic analysis was first undertaken many years ago by *H. Stetter*, and has now been carried out afresh by *H. W. Bergmeyer* in this new compilation, also published by Verlag Chemie. In collaboration with numerous other experts, he has produced a manual of modern practical procedures for quantitative analysis of biochemically important substances using enzymes, and for determining enzymatic activities in biological materials. We believe that this book represents a significant contribution to biochemical research. The importance of enzymatic methods of analysis can hardly be overrated. The effect of their introduction into experimental research bears comparison with the introduction of isotope techniques into biochemistry; their use in routine procedures is analogous to the value of using electrical calculating machines. The extended use of these methods of analysis, which are based on the pioneer work of *Otto Warburg*, has proceeded apace during the past ten years, alongside progress in many fields of biochemistry. As a result of the "information explosion", surveying the literature has become an impossible task in recent years, particularly since descriptions of methods of enzymatic analysis are strewn throughout the fields of biochemistry, nutritional chemistry, medicine, *etc.*

In this book, 115 authors, including many research workers of international repute, give astonishingly uniform and detailed descriptions of methods which they have personally developed or tested in practice.

Reference to this volume shows (a) whether a suitable enzymatic analytical procedure for assaying a given substance already exists, or if a biochemical method for estimating a given form of enzymatic acitvity has been worked out, (b) whether the method can be carried out with materials at hand, (c) how to carry out the test reliably without any additional information or any prior knowledge of the method, and (d) how to commence a search of original literature, thanks to the extraordinarily large number of literature references given. Moreover, many experimental details are given which are seldom or never to be found in the literature; several procedures have not previously been published.

The book is divided into four sections. In the first of these *H.U. Bergmeyer* describes the principles and practice of assay methods and *B. Hess* gives a succinct and comprehensive review of methods of cell and tissue breakdown. The main part of *Bergmeyer*'s contribution, as befits their importance, is taken up by an excellent presentation of photometric methods of measurement; manometry is discussed briefly and other techniques receive brief mention. Both authors describe most of the commercially available instruments, and the potentialities and limitations of experimental and theoretical sources of error are explained in detail. Since a major part of the book deals with assays of enzyme activities, it is perhaps recommendable that future editions should include reference to methods of assay of enzymes by immunological methods, even though these are not specifically within the scope of the book. This would asuredly contribute to avoidance of the still frequent practice of setting equal the measured enzymic activities to the generally unknown quantities of the given enzyme protein in protein mixtures of biological origin. The two following main sections contain practical procedures for the analysis of substrates (carbohydrates and phosphorylated derivatives, intermediary products of glycolysis and their derivatives, substrates of the citric acid cycle; proteins, peptides and amino acids; fatty acids and their intermediates, lipoids and steroids; nucleotides, purines, pyrimidines and co-enzymes; several inorganic substrates, and insecticides) and the determination of enzyme activities. Each contribution follows the same plan, describing in order, the principle of the method, the main reagents, their preparation and stability in solution, an example of the analysis, the method of calculation from the experimental measurements, and a discussion of sources of errors. Where a suitable enzyme preparation is not commercially available, a short description is given of a method for its purification, which can be applied directly. Not infrequently, the methods of purification given are improvements over published methods.

In the part on assays of enzyme activities, the importance of these methods in medicine is dealt with first (*E. Schmidt, F. W. Schmidt, H. D. Horn*, and *U. Gerlach*), and then, more briefly, their importance in nutritional chemistry (*J. Schormüller*) and in botany and agricultural chemistry (*E. Hofmann*). The contribution on medical aspects appears to us to be too extensive. The extent of enzyme activities in body fluids in the course and therapy of diseases of various organs and systems is described in an extremely detailed fashion, yet, for instance, there is no reference to the – in many respects extremely important – field of hereditary metabolic disorders. Already a relatively large number of these inborn errors of metabolism are known, in which the responsible enzyme defects have been identified. Nevertheless, a complete presentation of clinical enzymology would go far beyond the scope of this collection of practical methods and is not to be expected from the title. Subsequent contributions deal predominantly with the fields named above, and the section closes with microscopic-histochemical methods for identifying enzymes.

In the last part, *Bergmeyer* and co-workers deal with the properties of biochemical reagents (commercial enzymes, co-enzymes, and a few other substrates). The details of stability and quality standards given should prove especially useful. The short critical discussion of necessary and misleading purity declarations for commercial coenzymes and substrates is much to be welcomed.

This is not a book to fill the customary gap; it stands out on its own. It seems superfluous to wish the book a good circulation, for it is surely indispensible to all who carry out biochemical analysis either in the research or the routine laboratory. Moreover, it will contribute greatly to wider use of these methods.

Thanks are due, not least to the editor, for the extraordinary pains taken in the co-ordination of the large number of contributions; to the authors for the unusual liberality with which they have placed their practical knowledge at our disposal; and to the publishers for the excellence of the format, and, considering its content and size, the low price of the work.

U. Henning and *F. Lynen* [NB 933/31 IE]

[*] An English edition will be published jointly by Verlag Chemie and Academic Press (New York, London) in the Spring of 1963.

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Some Illustrative Applications of NMR Spectroscopy to Organic Chemistry [*]

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In recent years, a revolution in the practice of organic chemistry has been brought about by the application of physical methods. Nuclear magnetic resonance spectroscopy has been especially important in this regard, but so many papers have been published dealing with its uses in organic chemistry that any brief review such as this one can only cover illustrative examples. After a general introduction, attention will be focussed here on several interesting structural and dynamic problems involving or related to research being carried on in our laboratories.

Introduction

Nuclear magnetic resonance spectra result from absorptions of electromagnetic radiation in the radio-frequency range by magnetic nuclei in a magnetic field. Four types of nuclei can be differentiated with respect to their magnetic properties:

The members of the first class act as if they possess spherically symmetrical charge distributions but do not spin. Such nuclei, *e.g.*, ^{12}C, ^{18}O, *etc.*, have no magnetic moment and give no NMR spectra. These nuclei are said to have spin I equal to zero.

The second kind of nucleus acts as if it were spherically symmetrical and spinning, the circulation of charge giving rise to a magnetic moment. Such nuclei are assigned spin I of $^1/_2$ and include ^1H, ^{13}C, ^{19}F, *etc.*

For nuclei with spherically symmetrical charges, *i.e.* $I = 0$ or $I = {}^1/_2$, the electric quadrupole moment eQ is equal to zero.

The other two kinds of nuclei have $I > {}^1/_2$ and have ellipsoidal charge distributions, so that eQ is different from zero. The two types correspond to eQ being either positive or negative.

The present discussion will be concerned solely with nuclei having $I = {}^1/_2$ and particularly with ^1H, ^{19}F, and ^{13}C, which are of special interest in organic chemistry [1].

When a nucleus, such as a proton, with spin $^1/_2$ is placed in a magnetic field (Figure 1), it is found that there are only two observable orientations of the nuclear magnetic vector with respect to the applied field. These orientations correspond to magnetic quantum numbers, m, of $+{}^1/_2$ and $-{}^1/_2$. The $+{}^1/_2$ orientation is with the field

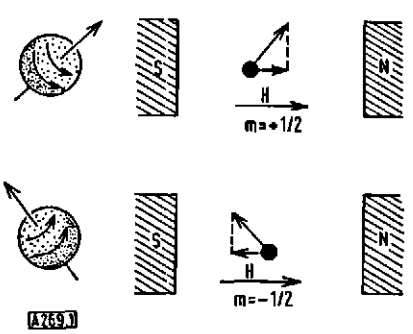


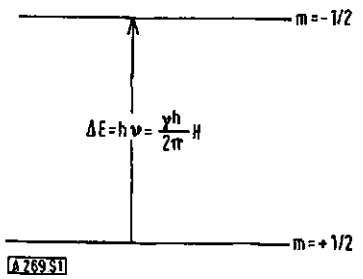
Fig. 1. Possible orientations of a nuclear magnetic moment in an external magnetic field of strength H, where the nuclear spin quantum number $I = {}^1/_2$.

(similar to a compass pointing north), and the $-{}^1/_2$ orientation is *opposed* to the field (pointing south). The magnetic quantum numbers then correspond to two energy levels – one favorable, the other unfavorable –

[*] Contribution No. 2909 from the Gates and Crellin Laboratories of Chemistry. This paper is adapted from lectures presented at the Butlerov Symposium, Leningrad, December 14th, 1961 and the 65th birthday celebration for Professor Dr. *G. Wittig*, Heidelberg, June 16th, 1962.

[1] Some effects of having $I > {}^1/_2$ and $eQ \neq 0$ are discussed in *J. D. Roberts:* Nuclear Magnetic Resonance Spectroscopy. McGraw-Hill, New York 1959, Chapter 5.

with an energy difference ΔE which depends on the nuclear properties (expressed by the gyromagnetic ratio γ) and on the strength of the applied field H (Scheme 1).



Scheme 1. Energy levels corresponding to nuclear magnetic spin quantum numbers of $m = +1/2$ and $m = -1/2$.

The energy difference between the two states corresponds to absorption of a quantum of electromagnetic radiation of frequency ν such that $\Delta E = h\nu$. To observe absorption, one must either adjust ν or H so that

$$\Delta E = (\gamma h/2\pi)H = h\nu \qquad (a)$$

Figure 2 shows as simply as possible how this might be done. A sample containing appropriate magnetic nuclei is subjected to radiation from a radiofrequency oscillator

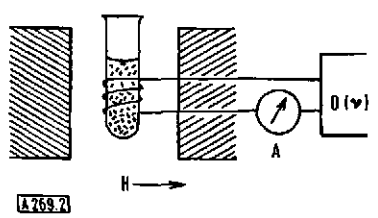


Fig. 2. Principle of a NMR spectrometer. O = High frequency generator, A = ammeter, H = direction of the external magnetic field.

at a fixed frequency ν. The magnetic field is then raised until ΔE has the proper value for absorption of energy to take place. When this occurs, additional current flows through the ammeter, *i.e.* resonance takes place. Further increase of the field makes ΔE greater than the proper value for resonance, so that the current falls to its

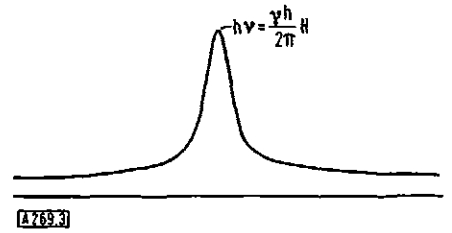


Fig. 3. Appearance of a NMR signal.
Ordinate: current strength.
Abscissa: strength H of the external magnetic field or frequency of the h.f. generator.

original value. The changes in the current illustrated in Figure 3 involve conditions where ν is kept constant and the magnetic field is changed. Alternatively, H can be kept constant and ν altered.

How is the nuclear magnetic resonance phenomenon of chemical interest? Figure 4 illustrates the principles involved in the chemical shift between different nuclei; the concept of the chemical shift is of great importance. The left-hand side of the figure shows a hypothetical nucleus with no surrounding electrons. The lines of force of the magnetic field at this nucleus will be unchanged from those of the applied field. The nucleus in

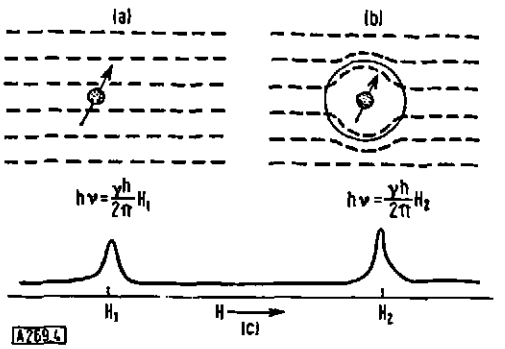


Fig. 4. Principle of chemical shift. (a) Hypothetical atomic nucleus without valence electrons; (b) atomic nucleus shielded by valence electrons in a magnetic field; the equations indicate the conditions for the occurrence of a resonance signal; (c) NMR spectra of the nuclei shown above. The distance between the two signals is called the chemical shift.

the right-hand side of the figure is the same except for the fact that it is surrounded by electrons. These electrons interact with the magnetic field so as to turn the lines of force outwards and make the field at the nucleus smaller in magnitude than the field of the magnet. The degree of this shielding effect will obviously depend on the electronic (chemical) environment of the nuclei. In this way, two nuclei of the same kind, such as protons, can give different resonance line positions, because a higher external magnetic field must be applied to the more shielded nucleus to bring it into the proper relationship between H and ν for resonance to occur. Thus, different line positions, or chemical shifts, are observed for nuclei in different chemical environments.

Figure 5 shows the proton NMR spectrum of a typical organic molecule, *viz.* 2-hydroxy-2-methylpentan-4-one,

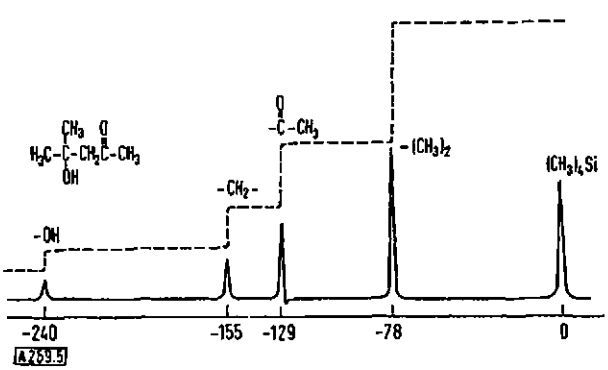


Fig. 5. Proton NMR spectrum of 2-hydroxy-2-methylpentan-4-one at 60 Mc/s and 14×10^3 gauss, with tetramethylsilane as internal standard. (- - -): Integral absorption intensity.
Abscissa: strength of the magnetic field referred to the position of the $(H_3C)_4Si$ resonance signal [c.p.s.]

at 60 Mc./s and room temperature with tetramethylsilane added to give an internal reference line for standardization of the line positions of the sample. The units of the abscissa are frequency units, *i.e.* cycles per second, but could of course be gauss [2]. The resonance line positions are clearly separated for the protons of the $-OH$, $>CH_2$, and the two kinds of methyl groups. It is possible to integrate electronically the area under each peak and one finds, as expected, areas in the ratios 1:2:3:6. The usual accuracy of such integrations is 0.5–1.0 %; this, of course, suggests a variety of analytical applications [3].

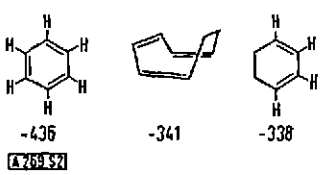
Table 1 shows a few typical proton chemical shifts with respect to tetramethylsilane as internal standard. The units here are c.p.s., and the variations from compound to compound for particular kinds of protons are usually

Table 1. Typical proton chemical shifts.
(C.p.s. at 60 Mc.p.s., $(CH_3)_4Si$ as internal standard).

$(CH_3)_4Si$	(0,0)	CH_3-O-	197
$CH_3-C<$	54	$CH_2=C<$	300
$-CH_2-$	75	H—O—R	330 [*]
$CH_3-C\equiv$	108	HAr	436
$H-C\equiv$	141	$H-C(=O)-R$	579

[*] Highly variable with temperature and concentration because of changes in the degree of hydrogen-bond formation.

± 5–20 c.p.s. [4]. Two typical uses of chemical shifts in structural problems might be mentioned. As shown in Scheme 2, the chemical shift of cyclo-octatetraene is



Scheme 2. Chemical shifts of proton NMR signals in systems with conjugated double bonds. Values in c.p.s. at 60 Mc/s with tetramethylsilane as internal standard.

very much more like that of 1,3-cyclohexadiene than that of benzene, thus confirming other evidence as to its general non-aromatic character [5]. Interesting studies of this type with other kinds of systems are being made by *Jackman*. A particularly important example is afforded by the NMR spectrum of the C_{18}-annulene *(1)*, a cyclic conjugated polyolefin with six hydrogens "inside" and twelve "outside".

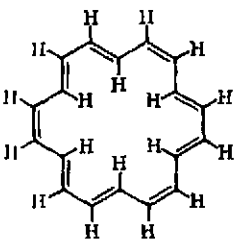
[2] The preference for c.p.s. units over gauss comes about because it is particularly easy to calibrate NMR spectra with the aid of side bands generated by an audio oscillator, the frequency of which is always expressed in c.p.s.; cf. Reference [3], Chapter 2.

[3] Cf. *J. N. Shoolery* in: NMR and EPR Spectroscopy. Pergamon Press, New York 1960, Chapter 8. This book contains much valuable practical information about NMR spectroscopy.

[4] An excellent summary of chemical shifts and a large number of illustrative proton spectra are contained in: High Resolution NMR Spectra Catalog. Varian Associates, Palo Alto, Calif., 1962.

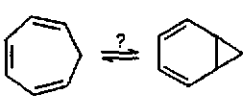
[5] *J. S. Waugh* and *R. W. Fessenden*, J. Amer. Chem. Soc. *79*, 846 (1957).

The external hydrogens have a chemical shift which is about 530 c.p.s. downfield from tetramethylsilane and which is thus similar to those of aromatic hydrogens; this substantiates the belief that the C_{18} annulene is


(1)

essentially aromatic in character. The internal hydrogens are strongly deshielded and their signal comes about 115 c.p.s. upfield from tetramethylsilane. This difference of over 600 c.p.s. between the resonance lines of the internal and external hydrogens can be correlated with diamagnetic effects produced by circulation of the π-electrons around the ring under the influence of the applied magnetic field [6].

Another intriguing structural problem is afforded by cycloheptatriene; *viz*, whether it is a single substance of structure *(2)*, or norcaradiene *(3)*, or a mixture of the



(2) *(3)*

two in more or less rapid tautomerism. NMR spectroscopy offers strong evidence for the triene structure for cycloheptatriene itself and for derivatives of the eucarvone type [7].

Spin-Spin Splitting

Figure 6 shows an important complication of NMR spectra, which can sometimes be annoying but which is usually extremely helpful, namely, "spin-spin splitting" (often called "spin-spin coupling"). These splittings arise from magnetic interactions between groups of magnetic nuclei. Here, protons are considered (X and Y are taken to be non-magnetic nuclei) in such a relationship that each proton group causes the other's lines to be split. In the first example, interaction between two single protons gives two doublets. In the second, two protons, H^1 and $H^{1'}$, cause a single-proton resonance (H^2) to be split into a triplet while the two-proton resonance (H^1 and $H^{1'}$) is in turn split by the single proton H^2 into a doublet.

[6] *L. M. Jackman*, quoted by *R. A. Raphael*, Proc. chem. Soc (London) *1962*, 104. For another example of the use of chemical shifts to determine aromatic character, in this case of pyridones, see *J. A. Elvidge* and *L. M. Jackman*, J. chem. Soc. (London) *1961*, 859.

[7] *E. J. Corey, H. J. Burke*, and *W. A. Remers*, J. Amer. chem. Soc. *77*, 4941 (1955); *K. Conrow*, *ibid. 82*, 5504 (1960); *83*, 2958 (1961); *R. Conrow, M. E. H. Howden* and *D. R. Davis*, *ibid.* in press; *W. v. E. Doering* and *M. R. Willcott, III*, Tetrahedron Letters *1962*, 663.

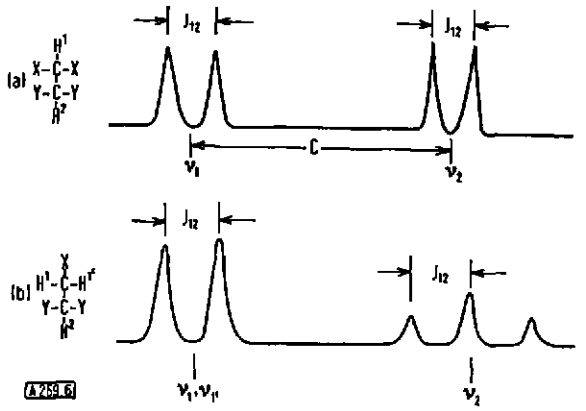


Fig. 6. Splitting of peaks by spin-spin coupling (a) between two protons and (b) between three protons. The length of the two-headed arrow C corresponds to the chemical shift.

The degree of spin-spin interaction is customarily denoted by the splitting constant J and is expressed in c.p.s. Space does not permit detailed discussion of the theory of spin-spin splitting [8]. In the particularly simple case of two protons, as at the top of Figure 6, where the chemical shift is large compared to J, the chemical shift difference $(\nu_2-\nu_1)$ leads to two main groups of lines. Each of these consists of two equally spaced lines. The chemical shift is easily recognized as such by the fact that the spacing between the main groups is directly proportional to the spectrometer frequency ν. In contrast, the splittings J_{12} are independent of ν and for this reason can easily be recognized also.

The splitting arises from changes in the total magnetic field produced at one proton by the magnetic moment of the neighboring proton and transmitted by the bonding electrons. Since the neighboring nucleus in any given molecule will have one of two possible orientations (corresponding to $m = +1/2$ or $m = -1/2$), there will be two lines observed for the other nucleus. One of these arises from those molecules in which the neighboring proton has $m = +1/2$, and the other from those molecules in which the neighboring proton has $m = -1/2$. The splitting J_{12} will be independent of the spectrometer frequency ν, because the magnetic moments of the interacting nuclei are independent of ν.

When there are two equivalent protons (*i.e.* equivalent in chemical shift) interacting with a third proton with a different chemical shift, the various possible arrangements of the magnetic quantum numbers lead to a characteristic 1:2:1 and a 1:1 pattern of resonance lines, as shown in the bottom of Figure 6.

The realization that the magnetic interaction between nuclei expressed by J may have either a positive or a negative sign has become more and more general. It is difficult to see without a detailed analysis how the sign of J can affect the spectrum. Indeed, there is no effect on the spectra of two nuclei with J positive or negative. However, with three nuclei arranged as, for example, in the fluorobenzene derivative *(4)* shown in Figure 7 (a so-called ABX system [8]), theory predicts that a switch between having both the J's for the fluorine-hydrogen interactions with the same sign to having them with differing signs may drastically alter the appearance of the spectrum [9]. The kind of change which occurs is illustrated for one particular set of parameters at the bottom of Figure 7.

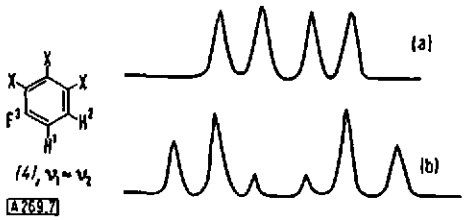


Fig. 7. Effect of the sign of the splitting constant J on the NMR spectrum; (a) signs of J_{13} and J_{23} identical; (b) J_{13} and J_{23} of different sign. The sign of J_{12} does not influence the spectrum.

Table 2 shows some typical J values for saturated compounds with normal bond angles. It can be seen that both positive and negative values of J are found and that these decrease with the number of bonds separating the hydrogens. In general, the signs of the coupling constants seem to alternate with the number of bonds. Thus, if two-bond J's are taken to be negative, three-bond couplings come out positive. Four-bond saturated couplings are small but probably negative. All of the J's shown in Table 2 are highly sensitive to molecular geometry [10], as will be seen in part from the following examples.

Table 2. Typical proton J values in saturated compounds

H –C– H	−10 c.p.s.	Strongly dependent on the H—C—H angle and the electronegativities of the attached groups
H H –C–C–	+ 7 c.p.s.	Sensitive to the dihedral angle between the H- C bonds as viewed along the C—C bond and to a smaller extent on the electronegativities of the substituent groups
H H –C–C–C–	−(?)0.5 c.p.s.	Seems to be largest if the protons are fixed in a *trans*-conformation

In Formula *(5)*, the side-chain couplings for α-methylstyrene dibromide [11] are shown; by analogy to other closely related systems [12], these can be expected to exist preferentially in the conformation shown. Note that the long-range four-bond coupling is 0.5 c.p.s. for *trans*-methyl to proton and zero for *gauche*-methyl to proton. The assignments were made on the basis of studies of stereospecifically deuterium-labelled compounds [11].

Evidence for different signs of the J values for two- and three-bond couplings in normal aliphatic compounds has been obtained in several ways. A typical example is

[8] See *J. D. Roberts:* An Introduction to the Analysis of Spin-Spin Splitting in High-Resolution Nuclear Magnetic Resonance Spectra. W. A. Benjamin, New York 1961.

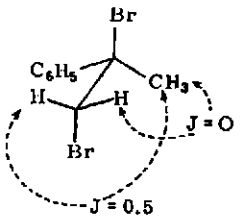
[9] Ref. [8], pp. 79–85; *H. S. Gutowsky, C. H. Holm, A. Saika,* and *G. A. Williams,* J. Amer. chem. Soc. *83*, 1306 (1961).

[10] See ref. [3], pp. 114–115 for an excellent brief summary of the angular dependence of J in aliphatic systems.

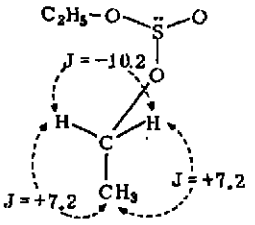
[11] *D. R. Davis* and *J. D. Roberts,* J. Amer. chem. Soc. *84*, 2252 (1962).

[12] *D. R. Davis, R. P. Lutz,* and *J. D. Roberts,* J. Amer. chem. Soc. *83*, 246 (1961).

provided by a detailed analysis of the spectrum of diethyl sulfite *(6)* [13]. It is not possible to analyse this spectrum by assuming that all of the J's have the same sign. It appears that this behavior is general [14].

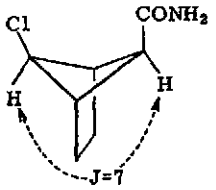


(5)

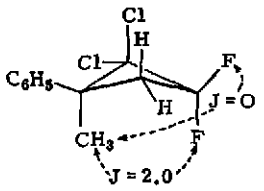


(6)

In Formula *(7)*, the extraordinarily large four-bond coupling discovered by *Meinwald* [15] for a strained bicyclic compound is shown. This is a *cis*-coupling; another very similar case has been found by *Wiberg* [16].



(7)

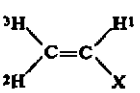


(8)

A similar five-bond hydrogen-fluorine coupling exhibited by the cyclobutane derivative *(8)* has been shown with stereospecifically deuterium-labelled compounds to be probably a *cis*-coupling also [17].

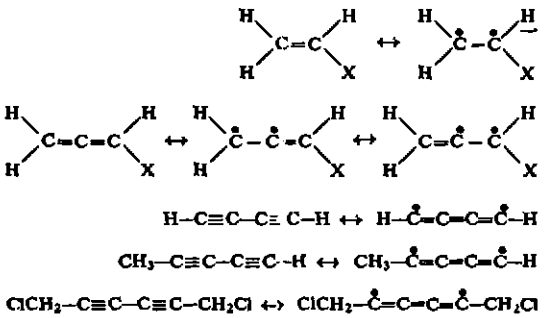
Table 3 shows some illustrative proton-proton J values for unsaturated systems [18]. Here, very long-range couplings are observed with both positive and negative

Table 3. Illustrative proton J values for unsaturated systems. All figures in c.p.s. The number of bonds between protons are in parentheses.

	J_{12}	J_{13}	J_{23}
	*ca.* 18(3)	12(3)	2(2)
H_3C–CH=C=CHCl (3) (2) (1)	−5.8(4)	+2.4(5)	+7.2(3)
H–C≡C–C≡C–H	2.2(5)		
H_3C–C≡C–C≡C–H	1.2(6)		
$ClCH_2$–C≡C–C≡C–CH_2Cl	1.0(7)		
H_3C–C≡C–C≡C–C≡C–CH_2OH	0.4(9)		

signs as well as important effects of geometrical configurations. Note the large differences between the three-bond *cis*- and *trans*-vinyl couplings and the much smaller two-bond geminal coupling. As an unsaturated chain is lengthened, the couplings decrease, but much more slowly than in saturated chains. The triacetylene at the bottom of Table 3 has an 0.4 c.p.s. coupling even though *nine* bonds separate the protons.

The magnitudes and signs of these couplings have been predicted theoretically by *Karplus* [19] by applying what amounts for practical purposes to consideration of the valence-bond structures shown in Scheme 3. Long-range couplings seem to be particularly strong in acetylenic and allenic derivatives, probably because these are rigid



Scheme 3. Radical resonance structures of olefins, cumulenes, and acetylenic compounds.

(minimum possible steric hindrance of resonance), and because the energy differences between the resonance structures (–C≡C– ↔ –Ċ=Ċ–) and (⟩C=C=C⟨ ↔ ⟩Ċ–Ċ=C⟨) are relatively less than for conjugated double or single bonds. In general, the more important the diradical resonance structures, the larger are the couplings.

Dynamic Effects

Perhaps the most interesting and exciting application of NMR is its use in the analysis of dynamic properties of organic molecules. A typical example, shown in Figure 8, involves the temperature-dependent fluorine

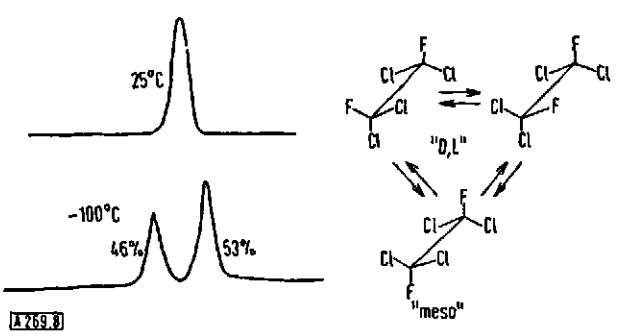


Fig. 8. ^{19}F NMR signals of 1,2-difluorotetrachloroethane at 25 °C and −100 °C.

resonance spectrum [20] of 1,2-difluorotetrachloroethane, a substance which would be expected to exist in three rotational conformations. However, such rotation should not be slow at room temperature. Observation of

[13] *F. Kaplan* and *J. D. Roberts*, J. Amer. chem. Soc. *83*, 4666 (1961).

[14] See *R. R. Fraser*, *R. U. Lemieux*, and *J. D. Stevens*, J. Amer. chem. Soc. *83*, 3901 (1961) and several more recent studies.

[15] *J. Meinwald* and *A. Lewis*, J. Amer. chem. Soc. *83*, 2769 (1961).

[16] *K. B. Wiberg*, *B. K. Lowry*, and *B. J. Nist*, J. Amer. chem. Soc. *84*, 1594 (1962).

[17] *M. Takahashi*, *D. R. Davis*, and *J. D. Roberts*, J. Amer. chem. Soc. *84*, 2935 (1962).

[18] Most of the values quoted are from *E. I. Snyder* and *J. D. Roberts*, J. Amer. chem. Soc. *84*, 1582 (1962).

[19] *H. S. Gutowsky*, *M. Karplus*, and *D. M. Grant*, J. chem. Physics *31*, 1278 (1959); *M. Karplus*, *ibid.* *30*, 11 (1959.

[20] *G. A. Thomas*, *D. R. Davis*, and *J. D. Roberts*, unpublished.

the rapidly equilibrating mixture of conformers at room temperature with a NMR spectrometer is found to give rather different results from those obtained with an infrared or ultraviolet spectrometer. The reason is that a NMR spectrometer requires a relatively long time to register measurements, somewhat like a camera with a rather long exposure time. Indeed, the "exposure time" is often about 0.001–0.01 sec. Now, if rotation about the C–C bond of 1,2-difluorotetrachloroethane occurs much faster than the period of observation, an average spectrum of all three conformers is observed, which corresponds to a single fluorine resonance line.

This is so at room temperature. However, as the sample is cooled, the rate of rotation becomes slower, and the NMR picture begins to blur (that is, the line broadens). At −100 °C, rotation is so slow that the separate resonance lines of the individual rotational isomers are observed (see Figure 8). Two of these isomers are mirror images (marked "D,L"), and their fluorine resonances coincide. The "*meso*"-isomer has differently located fluorines, and now the expected chemical shift difference is observed. It is interesting that the proportions of the rotational isomers are about equal; this is in agreement with electron-diffraction studies [21]. The rate of broadening of the resonance lines with temperature has been used to show that the activation energy of rotation E_a is about 8.4 kcal/mole [20].

A similar analysis is possible of the usually rapid interconversion of chair forms in cyclohexane derivatives. *Jensen* [22] studied cyclohexane itself, but more spectacular results have been obtained with the fluorine resonances of 1,1-difluorocyclohexane [23]. At + 35 °C, a fairly narrow quintet (due to hydrogen-fluorine coupling) is observed (see Figure 9), and on cooling to −40 °C, this gradually broadens to a wide low hump.

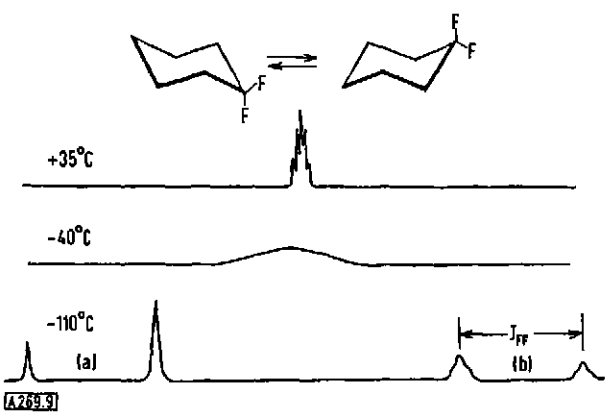


Fig. 9. ^{19}F NMR signals of 1,1-difluorocyclohexane at various temperatures; signals of (a) equatorial and (b) axial fluorine atoms.

At −110 °C, ring inversion is so slow that four principal lines are observed; these arise because the separate resonances of the equatorial and axial fluorines split one another. The chemical shift difference here, which corresponds to $(\nu_1-\nu_2)$ in Figure 6, is more than 800 c.p.s.

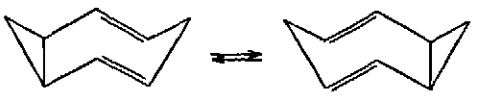
[21] *M. Iwasaki*, Bull. chem. Soc. Japan *32*, 205 (1959).

[22] *F. R. Jensen, D. S. Noyce, C. H. Sederholm*, and *A. J. Berlin*, J. Amer. chem. Soc. *82*, 1256 (1960).

[23] *K. Nagarajan* and *J. D. Roberts*, unpublished.

The activation energy E_a for inversion is calculated to be about 12 kcal/mole [23].

An extraordinarily interesting example of a highly mobile system of valence tautomers has been reported recently by *Doering* [24]; this involves bicyclo[7,1,0]-2,5-octadiene *(9)*. This substance gives a more or less featureless NMR spectrum at room temperature.



(9)

However, when the temperature is raised to 180 °C, a distinct averaged spectrum is produced, which shows absorptions corresponding to only two protons with typical vinyl chemical shifts. This indicates that the two valence tautomers are being interconverted rapidly.

At −50 °C, a very complicated spectrum corresponding to the conventional structure is observed.

Figure 10 shows another spin-spin splitting effect which can often be applied to great advantage. This is the splitting of proton and fluorine resonances by ^{13}C. The

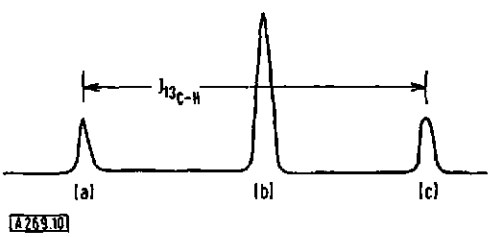


Fig. 10. Splitting of the proton NMR signal of ^{13}C-methyl iodide by the ^{13}C isotope. Peak (a): $H_3{}^{13}CI$ with $m_{^{13}C} = +1/2$, peak (b): $H_3{}^{12}CI$, peak (c): $H_3{}^{13}CI$ with $m_{^{13}C} = -1/2$.

effect is observed with ^{13}C with $I = 1/2$ but not with ^{12}C with $I = 0$ (and no magnetic moment). The splittings can be investigated using samples enriched in ^{13}C [25] or with a highly sensitive NMR apparatus using ^{13}C of natural abundance. In the latter case, the lines are usually quite weak (^{13}C is only 1.1 % in natural abundance) and are often called "^{13}C satellites", since they appear at $\pm 1/2\ J_{^{13}C-H}$ c.p.s. with respect to prominent proton resonance peaks. The spectrum of enriched ^{13}C-methyl iodide is used as an example in Figure 10. The center proton resonance line arises from ^{12}C-methyl iodide while the outer lines are the ^{13}C satellites corresponding to the ^{12}C magnetic quantum numbers of $+1/2$ and $-1/2$.

Figure 11 shows how $J_{^{13}C-H}$ is a function of the hybridization of the carbon atom involved [26]. In conjunction with $J_{^{13}C-H}$ for cyclopropane, this curve provides confirmation that the cyclopropane carbons are probably hybridized in much the same way as double-bond carbons; this is in agreement with much other

[24] *W. v. E. Doering*, Angew. Chem. internat. Edit., in the press.

[25] For an example of the use of the effect of ^{13}C on proton spectra in a tracer study, see *E. Renk, P. R. Shafer, W. H. Graham, R. H. Mazur*, and *J. D. Roberts*, J. Amer. chem. Soc. *83*, 1987 (1961).

[26] *N. Muller* and *D. E. Pritchard*, J. chem. Physics *31*, 768 (1959).

evidence. The very recent results of *Closs* [27] show that $J_{^{13}C-H}$ for the vinyl hydrogens in cyclopropenes is 220 c.p.s., a value which corresponds to 44 % s character for these C–H bonds, making them very much like acetylenic C–H bonds.

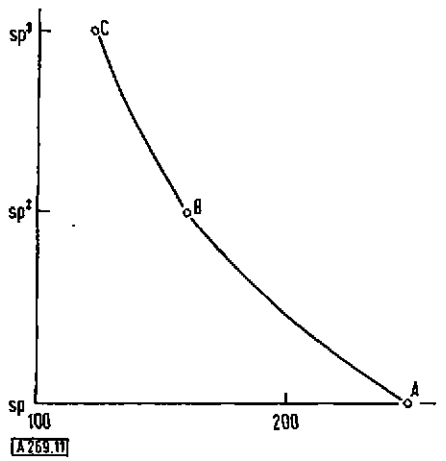
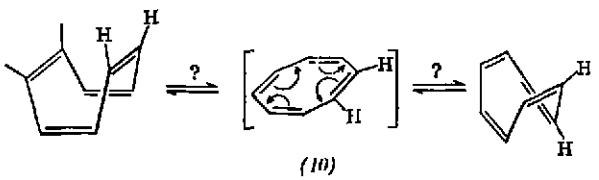


Fig. 11. Dependence of $J_{^{13}C-H}$ values on the hybridization of the ^{13}C atom.
A-acetylenic compounds; B-benzene; C-cyclohexane.
Ordinate: hybridization of ^{13}C atom.
Abscissa: $J_{^{13}C-H}$ [c.p.s.]

^{13}C satellite resonances have been recently applied to a previously unsolved problem, *viz.* how fast the double bonds in cyclo-octatetraene shift. Independent investigations [28] have shown that the ^{13}C satellites of cyclo-octatetraene are sensitive to temperature changes. At room temperature, the satellites are rather broad and not well resolved. However, at −40 °C they are considerably sharpened and show a different pattern. The most reasonable interpretation of this behavior is that it is the result of the slowing down of some dynamic equilibrium of cyclo-octatetraene. Most likely this is the shifting of the double bonds which might occur, as one possibility, by passage through the planar configuration *(10)*. These inferences based on the temperature dependence of the ^{13}C-satellites of cyclo-octatetraene have



(10)

been confirmed very recently by a study of fluorocyclo-octatetraene, which shows a very similar and very striking change in its fluorine resonance between room temperature and −80 °C [29].

New applications of nuclear magnetic resonance spectroscopy are being discovered almost daily, and yet there are many areas which need extensive investigation. Certainly the method has revolutionized and is still revolutionizing organic chemistry by permitting attack on more difficult and more subtle problems than ever before. The prospects for the future are very bright indeed.

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[27] *G. L. Closs*, Proc. chem. Soc. (London) 152 (1962).

[28] *F. A. L. Anet*, J. Amer. chem. Soc. *84*, 671 (1962); *G. M. Whitesides* and *J. D. Roberts*, unpublished.

[29] *D. E. Gwynn* and *J. D. Roberts*, unpublished.

Conductivity and Surface Chemistry of Crystals

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Doping of metals and semiconductors can change both their electrical conductivity and catalytic activity. The change in conductivity gives information about the number of occupied and vacant electron levels. If the rate-determining step of a catalytic reaction involving a doped solid can be identified, then a relationship between the conductivity and chemical behavior of the solid may be established.

Introduction

It is obvious that there must be some relationship between electrical conductivity on the one hand and the chemical behavior of surfaces on the other. This latter behavior, like all chemical properties, involves the formation and rupture of chemical bonds, be it within the lattice of the solid, at the boundary between the solid and a gas or liquid medium surrounding it (chemisorption, corrosion), or even within the molecule of a gaseous or liquid medium (catalysis). Our present knowledge of chemical bonds implies that rupture and formation of bonds entail charge exchanges, electron transitions between certain levels, and quantum mechanical resonances between electronic energy states. Hence, it is necessary to know something about these states. Using the postulates of theoretical organic

[*] Based on a lecture given in Aachen (Germany) on September 19th, 1961.

chemistry, it is possible to describe the energy states of molecules interacting, for example, with a surface. With regard to the states existing in the solid itself on the other hand, its electrical conductivity is one means of obtaining information about them.

There is no clear-cut relationship between the electrical conductivity of a solid and its chemical reactivity, in the sense that high conductivity is always associated with a chemically active surface. In fact, very often the opposite is true. Thus, for example, aluminum antimonide shows its optimum catalytic activity for decomposing hydrogen peroxide when its conductivity is at a minimum (provided the antimonide does have hole conductivity). Nevertheless, the relationships which do exist provide a deeper insight into the nature of the phenomena, even when they are of an inverse nature. In this sense, the chemist treats electrical conductivity as a heuristic tool – a stepping stone to further deductions about the nature of the solid – rather than as a property of direct use in chemical reactions.

Obviously, a direct relationship must exist between electrical conductivity and chemical reactivity when the charge transition or charge transfer in the solid is the rate-determining step of the reaction. This, for instance, is the case with tarnishing reactions: if metals are left to tarnish in a corrosive atmosphere (silver in chlorine, copper in oxygen), a thin compact layer of reaction product is first formed and the rate of further reaction becomes a function of the rate of metal ion transport across this layer. However, this ion transport also determines the rate of electrical conduction through the layer of silver chloride or cuprous oxide. Obviously, the rate of reaction is directly related to the conductivity in these cases. This dependence is given by the Nernst-Einstein relationship between the diffusion coefficient and the conductivity coefficient, and *Carl Wagner* was in fact able to predict tarnishing rates from measurements of the conductivity and the transference number in numerous cases. The results were at first derived directly from the ionic conductivity. Similar relations always hold for electronic conductivity of a tarnish layer, provided the ion transport creates a space charge. In fact, the positive charge density increases with the continued diffusion of ions outwards into the external layer. The electrostatic field of opposite sign finally stops the ion diffusion, and this causes deviations from the Tammann parabola, that is, anomalous tarnish reactions appear. It is now known that these deviations result in many instances simply because the electron conductivity is not high enough, so that the space charges built up by the chemical reaction are not neutralized fast enough. Under these conditions, the electron conductivity determines the rate of a chemical reaction.

Electronic States of Metals and Semiconductors

Let us now consider cases in which electrical conductivity yields information on the electronic states in a solid which are associated with a rate-determining step of a chemical reaction. Solids can, in general, be classified as metals (at ambient temperatures, free electrons are able to move in electric fields) and semiconductors (electrons or holes move only at higher temperatures). The electrons of a free metal atom can exist in the so-called K, L, and M shells or energy levels. If the atoms are part of a crystal structure, each of these levels must split in order to conform with the Pauli principle, *i.e.*, these shells degenerate. In addition, their energies will depend on the distance between the atoms in the crystal structure. When the correct interatomic distance is reached, overlapping energy bands replace the discrete levels. These bands contain the same number of electrons as were originally present in the corresponding discrete shells of the atoms. In metals with electrons in an S subshell (S-metals) such as copper, silver, or gold, only the last conduction or valence electron is spread into a band. Such a band may contain as many as two electrons per atom, since each level can be filled with two electrons of antiparallel spins. However, only one electron is present, *i.e.*, the band is only half-filled. This situation yields highest conductivity. If such a metal is doped with foreign metals, the band becomes populated with more electrons and the conductivity decreases. Stated in crude terms, the number of vacancies available for occupancy by field-accelerated electrons, decreases. In more sophisticated terms, this statement means that the Fermi limit is being approached, and that the density of available electron levels decreases.

It is worth pointing out that the electron population of the conduction band determines the phase of a metal. Electrons can enter a given phase only until the momentum of the fastest and most energy-rich electron is sufficiently large and until the corresponding conjugate length of the electron wave has become sufficiently small to cause Bragg reflection in the crystal lattice. Once this has happened, the electron is no longer a part of the electron gas, the phase becomes unstable and a new phase appears. This explains, for instance, the successive appearance, at specific electron concentrations, of α-, β-, and γ-phases in the Hume-Rothery alloys.

Semiconductors differ from metals in that the bands created by splitting of electron levels do not overlap but are separated by considerable energy gaps. We speak here of a "valence band", in which the electrons are associated with individual chemical bonds, ions, or atoms, and of a "conduction band", in which, generally speaking, there are no electrons. If the valence band is occupied and the conduction band is empty, the solid is an insulator. If, by some means, electrons are transferred to the conduction band, the solid becomes a semiconductor. The higher the temperature, the greater the number of electrons present in thermal equilibrium within the conduction band, hence semiconductors have increased conductivities at higher temperature. Obviously, holes in the valence band could just as well have been discussed instead of electrons in the conduction band.

Another possibility is to "dope" pure substances, *i.e.*, to introduce electron acceptors to remove electrons from the valence band ("p-doping"), or to place electron donors in the forbidden zone in order to supply electrons to the conduction band ("n-doping").

Again, a semiconductor can be regarded as a chemical system: one might then inquire about the chemical meaning of the band of valence electrons. Figures 1a and 1b show a scheme according to *Carl Wagner* representing p- and n-conducting inorganic compounds,

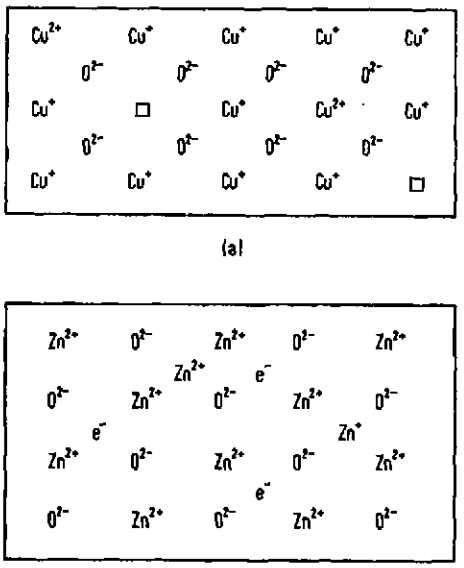

Fig. 1a. Lattice defects in cuprous oxide, after *C. Wagner*. The copper deficit in CuO_2 produces equivalent numbers of vacant Cu^+-positions (□) and Cu^{2+}-ions (electron holes).

Fig. 1b. Lattice defects in zinc oxide containing an excess of zinc (occupation of intermediate structure positions; equivalent number of quasi-free electrons).

e.g. cuprous oxide, Cu_2O (which is p-conducting), and zinc oxide, ZnO (which is n-conducting). In physical terms, p-conduction implies the presence of acceptors in the forbidden zone. Chemically the Cu^{2+} ions which, strictly, do not belong in cuprous oxide, may act as if they were holes, *i.e.*, acceptors able to receive electrons from neighboring ions of the crystal lattice. As a result, the hole becomes mobile and may migrate through the structure. In the opposite case of n-conducting oxides such as ZnO, donors are present in the forbidden zone. The chemist says that there are Zn ions with a positive-charge deficiency, *i.e.*, ions with too many electrons in the intermediate structure. At higher temperatures these become dissociated, *i.e.*, the donors release electrons into the conduction band and become normal Zn ions within the crystal lattice. As a result, electrons begin to migrate.

Conductivity and Chemical Behavior

In the light of the foregoing discussion, it is seen that the main problem is to relate electronic phenomena in metals and semiconductors (as implied by their conductivity) to the chemical properties of the substances. Attempts have been made over many decades to investigate the electronic states of various substances by means of conductivity and compare the chemical behavior of the substances with each other. The results obtained are very reasonable: for example, it is obvious why sodium reacts with oxygen in air, whereas silver does not, if one compares the state of the conduction bands of sodium and silver crystals in a vacuum. The energy required for the release of an electron from silver is much greater than that for sodium. Hence, sodium is transformed more easily into the ionic state. However, this method fails if one wants to study more detailed relationships.

For years, we and many others have tried to explain the catalytic decomposition of either formic acid or ethyl alcohol in the presence of various metals on the assumption that the sequence of activation energies must somehow be related to the respective electrical conductivities or to the energy required for electron release, *i.e.*, to the states of the highest energy levels which are still occupied. We were, however, unable to find such a relationship. Copper, silver, and gold conform to the stated assumption, whereas palladium and nickel do not. With oxides or other compounds, the situation is even more complicated. Obviously, the electronic factor is not the only one determining chemical behavior at surfaces. Many other things must be important, in particular, parameters which we call geometric factors, *i.e.*, the dimensions and energy of the crystal lattice. The difference between gold and nickel or zinc does not rest solely upon the electron population at various levels of the conduction band: many geometric parameters are also different.

Investigations on Doped Solids

The problem was solved by a new principle which we could have learned from the physicists long ago: the principle of doping, *i.e.*, the introduction of an electron donor or acceptor into the forbidden zone of a semiconductor, or, in the case of a metal, the shifting of the Fermi limit of the highest occupied level in the conduction zone. Doping can be accomplished with very small additions. This means that the solid (or in the case of catalysis, the solid catalyst) retains its nature almost completely: the crystal structure, the chemical behavior, the position of the bands, and the lattice symmetry remain the same; only the electronic factor changes, and it changes in the manner desired by the investigator. It is now possible to make comparisons. For instance, a semiconducting oxide containing donor or acceptor substances that tend to increase its conductivity may be compared with the same oxide in a state of lower conductivity, and appropriate conclusions may be drawn. This principle of doping has added more to the understanding of the catalytic activity of metals and semiconductors, and of the chemical reactions and the surface behavior of these systems, than comparisons of different metals and compounds.

The following sections present examples of these results and relate the chemical behavior of the surface and the conductivity. Table 1 shows an attempt to systematize the influence of donor or acceptor substances on con-

Table 1. Conductivity and catalytic activity of metals and semiconductors as a function of doping. The direction of the arrows indicates whether an increase or a decrease in the value of a property occurs as a result of doping. Arrows in brackets mean that the prediction has not yet been verified experimentally.

	Doping agent: Higher valence			Doping agent: Lower valence		
	Conductivity	Catalysis: Donor reaction	Catalysis: Acceptor reaction	Conductivity	Catalysis: Donor reaction	Catalysis: Acceptor reaction
Metals with Brillouin zone more than half-filled	↓ Cu/Sn ↓ Cu/Zn Ag/Pb Ag/Cd	↓ HCO_2H-decomposition on Ag/Me [*] CH_3OH-decomposition on Ni/Cu C_2H_4-hydrogenation on Ni/As	(↑)	↑ Ag/Pd	↑ HCO_2H-decomposition on Ag/Pd CO-oxidn. on Ag/Pd p-H_2-conversion on Cu/Ni	↓ H_2O_2-decomposition on Cu/Ni
Metals with Brillouin zone less than half-filled	↑ Sn liq./Sb (provided there are no localized bonds)	↓ HCO_2H-decomposition on Sn/Sb (provided there are no localized bonds)	(↑)	(↓)	↑ HCO_2H-decomposition on Sn liq./Cu	(↓)
Semiconductors (p-type conductors)	↓ NiO/Cr_2O_3	↓ CO-oxidn. on NiO/Cr_2O_3 C_2H_4-hydrogenation on Ge/As	(↑)	↑ NiO/Li_2O	↑ CO-oxidn. on NiO/Li_2O C_2H_4-hydrogenation on Ge/In	↓ H_2O_2-decomposition on AlSb/In
Semiconductors (n-type conductors)	↑ ZnO/Ga_2O_3	↓ N_2O-decomposition on TiO_2/WO_3	↑ CO-oxidn. on ZnO/Ga_2O_3	↓ ZnO/Li_2O	↑ N_2O-decomposition on TiO_2/Li_2O C_2H_5OH-oxidn. on ZnO/Li_2O	↓ CO-oxidn. on ZnO/Li_2O

[*] Me stands for metals with a higher valence than silver.

ductivity and on chemical and catalytic properties. This Table is very crude, but it gives a general idea of the field. It is valid only if all side-effects can be neglected. These side-effects are partially accounted for, *e.g.*, when stated "provided there are no localized bonds".

The following conclusions can be drawn from Table 1: metals and semiconductors can be doped in two different ways. One can introduce substances of higher valence, *e.g.* zinc or tin into copper, or chromium oxide into nickel oxide. Alternately, substances of lower valence can be added, *e.g.*. palladium to silver, or lithium oxide to zinc oxide. In either case, changes in conductivity result, as indicated by the arrows. With semiconductors, one must, of course, differentiate between p- and n-conductors, and with metals, whether the Brillouin zone, *i.e.* the conduction zone, is more than half-filled, in which case adding more electrons decreases the conductivity, or less than half-filled, when adding electrons increases the conductivity. Hence, the conductivity is reduced if elements of higher valence, such as zinc or tin, are introduced into copper, since its conduction zone is already more than half-filled. On the other hand, in tin, the conduction zone of which is far from being completely occupied because of the overlap in the conduction bands, addition of more electrons results in higher conductivity, while introduction of lower valence ions brings about the opposite effect.

The situation is very similar with semiconductors: doping nickel oxide with chromium oxide decreases its conductivity; addition of gallium oxide or chromium oxide to zinc oxide increases its conductivity.

The Table also indicates what will happen in the case of catalysis, provided a donor or acceptor reaction is involved. In donor reactions, penetration of electrons into the solid as a consequence of the activation results; the reverse is true in acceptor reactions. Donor reactions are, as a rule, either hydrogenations or dehydrogenations: acceptor reactions are, generally speaking, either oxidations or deoxidations. On this basis, one would expect that the effectiveness of a substance as a catalyst in a donor reaction will increase with any decrease in the number of its electrons. On the other hand, donor reactions will be poorly catalysed by a copper catalyst doped with elements of higher valence. Increases in the activation energies for the decomposition of formic acid, the decomposition of methanol, and the hydrogenation of ethylene are in fact, observed if the copper is doped with elements of higher valence. For the same reason, titanium dioxide is less efficient as a catalyst for the decomposition of nitrous oxide when it has a higher conductivity: the decomposition is a donor reaction in which electrons are given up to the catalyst. This transfer requires more energy when the catalyst is already well supplied with electrons.

There are also exceptions to these rules: molten tin should give a higher conductivity when doped with elements of higher valence. In practice, however, a lower conductivity is found. The reason for this is that the impurities do not dissolve in the tin to form an alloy, but produce localized bonds, *i.e.*, tin-bismuth or tin-antimony molecules are formed. Thus the number of electrons decreases, instead of rising.

The following figures show some specific examples. Figure 2 gives the activation energy of the donor reaction $HCO_2H \rightarrow H_2 + CO_2$ on a silver catalyst containing elements of higher valence. The energy increases since on doping the electron concentration goes up, whereas the number of vacant electron levels in the conduction zone decreases. For the same reason, the activation energy increases systematically with the position of the doping substance in the periodic table [1]. This position is represented by the number n, and the square root of the increase of activation energy is linearly proportional

[1] *G. M. Schwab*, Trans. Faraday Soc. *42*, 689 (1946).

to n. For instance, n = 1 represents zinc or cadmium, n = 2 represents gallium or indium, *etc.* It is known that the α-phase appears in the system copper/tin up to 1.3

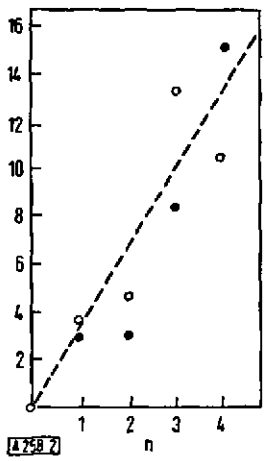

Fig. 2. Activation energy for the donor reaction $HCO_2H \rightarrow H_2 + CO_2$ on silver catalysts doped with elements of higher valence from the 4th (o) or 5th (●) Period.

Ordinate: square root of the increase of the activation energy $(\Delta A)^{1/2}$ $[(kcal/mole)^{1/2}]$.

Abscissa: position of the doping element in the periodic table (see text)

electrons/atom. The activation energy of a donor reaction increases within this α-phase (Figure 3). At 1.6 electrons/atom, the γ-phase appears; at 1.75 electrons/atom, the ε-phase; at 2.4 electrons/atom, the η-phase.

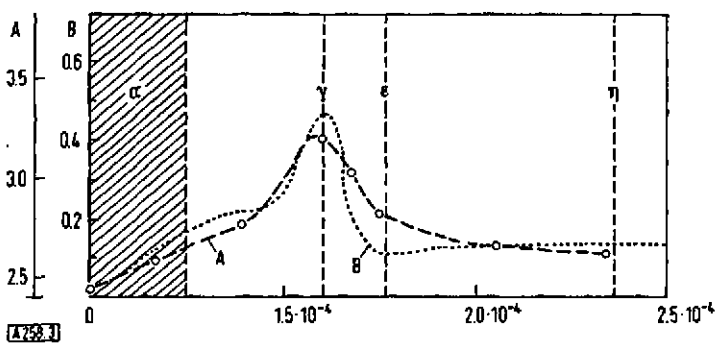

Fig. 3. Activation energy of the reaction $HCO_2H \rightarrow H_2 + CO_2$ (A) and electric resistivity (B) as functions of electron concentration in the system Cu/Sn.

Ordinate: (A) activation energy [kcal/mole], (B) electric resistivity [Ohm · cm].

Abscissa: electron concentration [electrons/atom].

Figure 3 shows that the activation energy in the γ-phase passes through a maxium [2]. There are many other examples in which this maximum also occurs at the γ-phase. The dotted line shows the dependence of the electric resistivity on the electron concentration. A similar maximum appears, *i.e.*, resistivity and activation energy behave in the same way. This statement is equivalent to saying that catalysis and conduction are parallel phenomena. The theory of metals postulates that the γ-phase will coincide with the resistivity maximum, because there are extremely few unfilled levels. Thus, the catalysis is here associated with these unfilled levels.

[2] *G.-M. Schwab* and *A. Karatzas*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *50*, 242 (1944).

In Figure 4, the conductivity of molten tin is plotted *vs* the antimony content. A solid intermetallic compound is formed at an antimony content of 0.30 atom percent. Antimony decreases the conductivity, since it needs electrons in order to form covalent bonds. Figure 5 shows that, for this same reason, the activation energy for the decomposition of formic acid (a donor reaction)

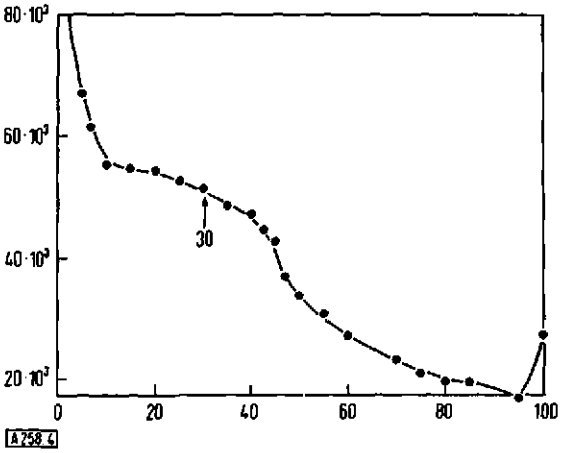

Fig. 4. Electric conductivity of the system Sn/Sb at room temperature.
Ordinate: conductivity [mho/cm].
Abscissa: antimony content [atom percent].

also decreases. The addition of copper results in only a very minor decrease, which is probably also caused by the formation of covalent bonds [3].

Doping zinc oxide with lithium oxide results in a decrease in the number of free electrons and in the conductivity while addition of gallium, on the other hand, leads to an increase in conductivity (Figure 6a). The activation energy for oxidation of carbon monoxide

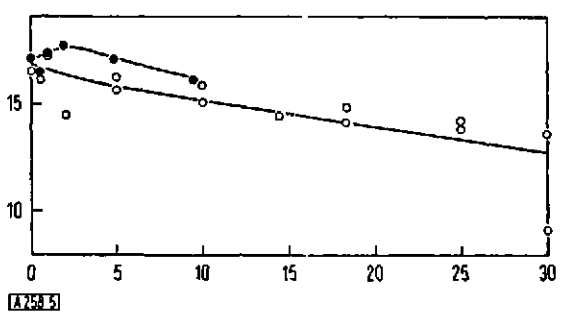

Fig. 5. Activation energy of the reaction $HCO_2H \rightarrow CO_2 + H_2$ in the presence of liquid Sn doped with Cu (●) or Sb (o).

Ordinate: activation energy [kcal/mole].

Abscissa: Cu or Sb content [atom percent].

[3] *G.-M. Schwab*, Dechema-Monogr. *38*, 205 (1960).

also decreases, *i.e.*, the catalysis becomes more efficient with higher conductivity (Figure 6b). In this semiconductor (ZnO) the quasi-free electrons determine catalytic behavior. Hence, oxidation of CO is an

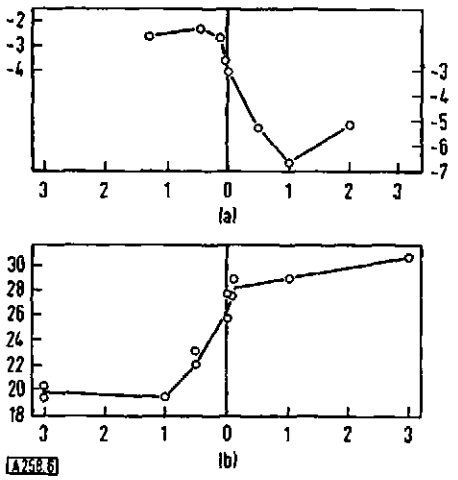

Fig. 6a. Electric conductivity of doped zinc oxide.

Ordinate: log k [mho/cm].

Abscissa: (center to left): gallium oxide content [mole percent]; T = 600 °C; pO_2 = 1 atm.
(center to right): lithium oxide content [mole percent]; T = 394 °C; pO_2 = 0.2 atm.

Fig. 6b. Activation energy for the oxidation of carbon monoxide in the presence of doped zinc oxide.

Ordinate: activation energy [kcal/mole].

Abscissa: (center to left): gallium oxide content [mole percent]; (center to right): lithium oxide content [mole percent].

acceptor reaction. In the system carbon monoxide/oxygen, the oxygen is of course the acceptor. The reaction rate should, therefore, be proportional to the partial pressure of the oxygen; this is in fact, confirmed by experiment [4].

Adding lithium oxide to a p-type conductor such as nickel oxide results in an increase in the number of holes – and thus in higher conductivity – as well as a more efficient catalysis of the oxidation of carbon monoxide, *i.e.*, a lower activation energy. In this case, the electron holes determine the effectivity of catalysis. The carbon monoxide is the electron donor, and the reaction rate is thus proportional to the partial pressure of the carbon monoxide and independent of that of the oxygen [4].

Another example of a donor reaction is the decomposition of nitrous oxide. It is catalyzed not only by p-type conductors (analogous to the CO oxidation), but also by n-type conductors (Figure 7). Adding lithium oxide to the zinc oxide catalyst also results in a decrease of the number of free electrons. In this case, however, it is accompanied by a decrease in the activation energy. The decomposition of N_2O is a donor reaction, since desorption of the oxygen which is formed on decomposition and which is chemisorbed in the process is the rate-determining step. The oxygen must lose one electron in order to be able to leave the surface. Such a process becomes increasingly unlikely with rising electron concentrations in the catalyst [4].

[4] *G.-M. Schwab* and *J. Block*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *5*, 756 (1954).

It has been shown by experiments in which electrons are promoted into the conduction band not by heating (as in thermal catalysis) but by irradiation with ultraviolet light, which is absorbed by the zinc oxide, that it is

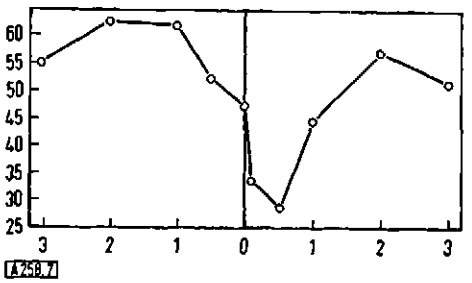

Fig. 7. Activation energy for the decomposition of nitrous oxide in the presence of doped zinc oxide.

Ordinate: activation energy [kcal/mole].

Abscissa: (center to left): gallium oxide content [mole percent]. (center to right): lithium oxide content [mole percent].

really the electrons in the conduction band that determine the chemical behavior of zinc oxide. By them the acceptor molecules, such as oxygen, may be catalytically activated: when zinc oxide is shaken in methanol (Figure 8) or ethanol and subsequently irradiated,

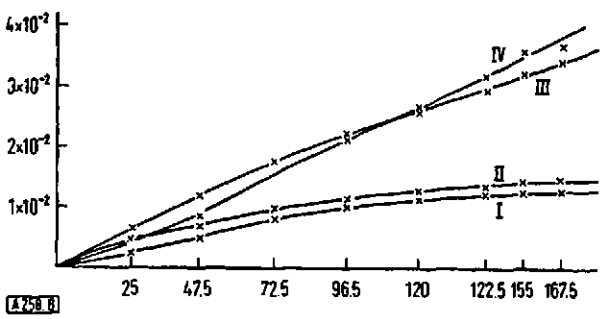

Fig. 8. Oxidation of methanol in the presence of zinc oxide or zinc sulfide under irradiation with ultraviolet light.

Curve I: ZnO
Curve II: ZnS
Curve III: ZnO (twice the amount as for curve I)
Curve IV: ZnS (twice the amount as for curve II)

Ordinate: O_2 consumption [cm³].

Abscissa: time [hours].

oxygen absorption results. Formaldehyde and formic acid, or acetaldehyde and acetic acid are the products found in the solution. In this reaction, the zinc oxide is therefore a solid triggering the spontaneous photochemical oxidation. It is, of course, possible to induce a non-spontaneous reaction. For instance, it is possible to produce hydrogen peroxide from oxygen and water in the presence of irradiated zinc oxide [5].

Elemental semiconductors, such as germanium or silicon, or compounds such as aluminum antimonide can be made either p- or n-conducting by doping. Characteristic differences in chemical behavior, depending only on the type of conduction, are obtained. Figure 9 shows the hydrogenation of ethylene in the presence of germanium which contains a fraction of a permille of doping substances. There are significant

[5] *G.-M. Schwab*, Advances Catalysis related Subjects *9*, 229 (1956).

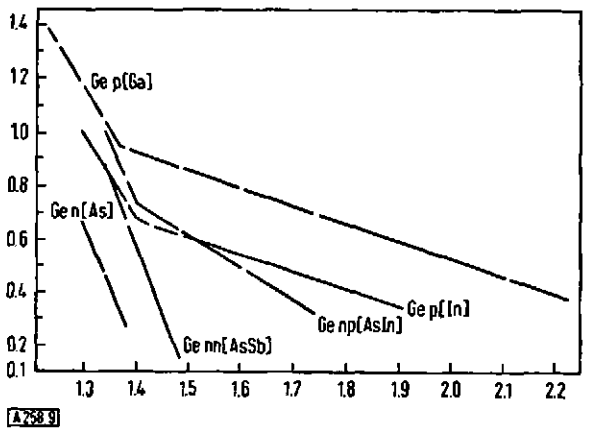

Fig. 9. Hydrogenation of ethylene in the presence of doped germanium.
Ordinate: reaction rate [arbitrary units].
Abscissa: $1/T \times 10^3$ [(°C)$^{-1}$].

differences between the p-state and the n-state: p-type germanium, obtained either by doping with indium or gallium or from n-type germanium originally doped with arsenic and then switched to the p-state by overdoping with indium, induces hydrogenation of ethylene at a very low activation energy and at temperatures close to room temperature. With n-type germanium doped with arsenic or antimony on the other hand, the activation energy is considerably higher and hydrogenation does not start until 400 to 450 °C is reached [6].

Semiconductors can be used not only as catalysts, but also as carriers for catalytically active material. The latter application is of considerable practical importance. Carriers are catalytically inactive. Aluminum oxide does not affect formic acid up to 300 °C. However, a deposit of nickel, cobalt, or silver on the aluminum oxide is by nature catalytically active for hydrogenating ethylene or decomposing formic acid (Figure 10). The activation energy of these reactions can be influenced by doping the carrier instead of the metal. In the case shown in Figure 10, aluminum oxide has been doped

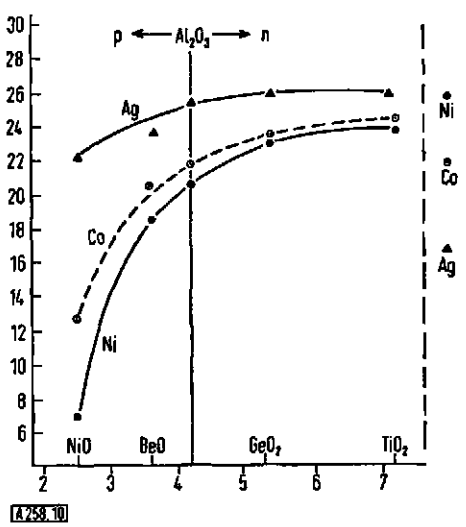

Fig. 10. Activation energy of the reaction $HCO_2H \rightarrow H_2 + CO_2$ on various doped aluminum oxides with metal coating. Extreme right: activation energy for the reaction on compact metals.
Ordinate: activation energy [kcal/mole].
Abscissa: electrical conductivity of the carrier [$\times 10^6$ mho/cm].

[6] *G.-M. Schwab, G. Greger, St. Krawczynski,* and *J. Penzkofer,* Z. physik. Chem. N. F. *15*, 363 (1958).

with oxides of higher valence, increasing its conductivity. Similarly, adding oxides of lower valence decreases its conductivity [7].

Not only catalytic reactions but also surface reactions in which the solid itself is a reactant can be better understood by considering conductivity. Figure 11 illustrates the reaction between pulverized zinc oxide

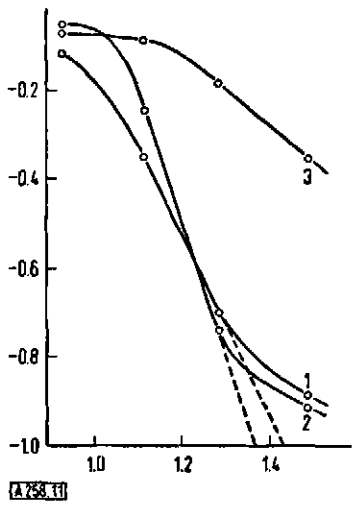

Fig. 11. Rate of the reaction between solid ZnO and solid $CuSO_4$ as a function of ZnO doping.
Curve 1: ZnO.
Curve 2: ZnO + 1 % Ga_2O_3.
Curve 3: ZnO + 1 % Li_2O.
Ordinate: logarithm of the reaction rate.
Abscissa: $1/T \times 10^3$ [(°C)$^{-1}$].

and pulverized anhydrous copper sulfate. The reaction is spontaneous and complete, resulting in copper oxide and zinc sulfate. With pure zinc oxide (Curve 1), an activation energy of 25 kcal/mole is observed. This energy is required to make zinc ions diffuse out of the lattice and into the copper sulfate crystal and to envelope the crystal and form copper oxide and zinc sulfate. If, however, the zinc oxide is doped with gallium oxide so that its conductivity increases owing to an increased number of donors or quasi-free electrons in the lattice, the reaction becomes slower. Curve 2 is steeper, *i.e.*, a higher activation energy (36 kcal/mole) is required. Thus, activation of the conductivity in this instance results in deactivation of the surface reaction, since there is an equilibrium between the quasi-free electrons and the ions within the crystal lattice. This follows from the Wagner-Schottky theory of crystal defects. If the doping substance is lithium oxide, the activation energy is only 8 kcal/mole, since this type of doping results in a considerably larger number of zinc ions being in intermediate structure positions than in pure zinc oxide (Curve 3) [8].

Similar relationships may be expected to exist between the chemical activity and conductivity of ion conductors. Lead chloride, for instance, is a pure anion conductor in which the chloride ions move and undergo reactions

[7] *G.-M. Schwab, J. Block,* and *G. Schultze,* Naturwissenschaften *44*, 482 (1957); Angew. Chem. *71*, 101 (1959).

[8] *G.-M. Schwab* and *M. Rau,* Z. physik. Chem. N. F. *9*, 127 (1956); ibid. *17*, 257 (1958).

because of the presence of anion holes. Replacement of bivalent lead cations with monovalent ions, for instance, by introducing potassium chloride, should lead to an increase in the number of anion holes, making the reaction $PbCl_2 + BaO \rightarrow BaCl_2 + PbO$ more probable. Anions of higher valence, such as sulfides, sulfates or phosphates should act in the same way. Figure 12 shows that this is indeed observed. It is shown in Figure 13

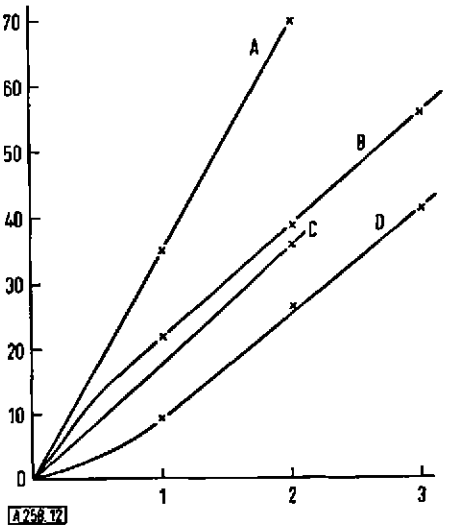

Fig. 12. Reaction of doped $PbCl_2$ with BaO.
Curve A: addition of $Pb_3(PO_4)_2$; difference in anion charge = +2.
Curve B: addition of KCl; difference in cation charge = −1.
Curve C: addition of PbS; difference in anion charge = +1.
Curve D: addition of $LaCl_3$; difference in cation charge = +1.
Ordinate: decrease in the temperature at which the reaction starts [°C].
Abscissa: content of doping substance [mole percent].

that changes in anion conductivity follow the same rules [9]. However, a certain anomaly occurs when La^{3+}-ions are introduced as impurities. Decrease of the chloride ion holes and thus, retardation of the reaction is to be expected. The experimental results confirm this expectation at very low concentrations of the doping agent. However, the reaction rate increases with rising of the doping substance. This behavior can only be explained by assuming that the lead cations become mobile owing to an increase in the number of cation holes. *G. Eulitz* of this Laboratory succeeded recently in showing by transference measurements that the lead ions do indeed migrate, if the lead chloride is doped with lanthanum.

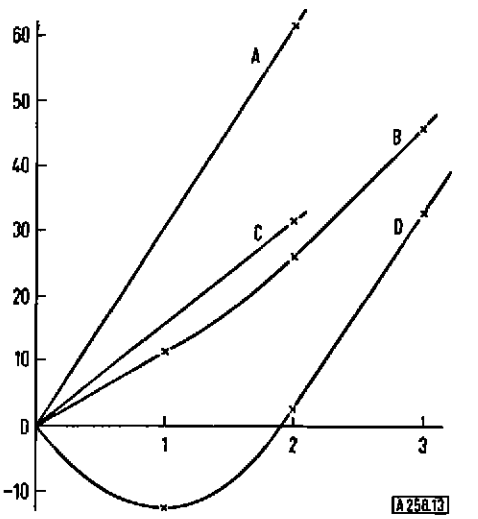

Fig. 13. Conductivity of doped $PbCl_2$.
Curve A: addition of $Pb_3(PO_4)_2$.
Curve B: addition of KCl.
Curve C: addition of PbS.
Curve D: addition of $LaCl_3$.
Ordinate: decrease in the temperature at which conduction starts [°C].
Abscissa: content of doping substance [mole percent].

Conclusions

The general conclusion is that several factors must be taken into account if one wants to formulate relationships between surface chemistry, catalysis, solid-phase reactions and conductivity which will agree with experimental results. Doping may be used to change the conductivity, and the changes in conductivity may be used to draw reasonable conclusions concerning filled or unfilled electron levels in the solid under investigation. In the case of chemical reactions involving doped solids, it is necessary first to identify the rate-determining steps by means of kinetic measurements. Only then is it possible to relate, in a logically consistent manner, the conductivity of a solid and its chemical properties. From this type of investigation, one obtains information on the number of electrons in the quantum states of the solid and, thus, on the role of the electrons in solid-phase chemical reactions.

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[9] *G.-M. Schwab* in *J. H. de Boer:* Reactivity of Solids. Elsevier, Amsterdam 1960, p. 392.

Reactions of Graphite with Metal Chlorides

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Dedicated to Prof. Dr. Ulrich Hofmann on the occasion of his 60th birthday

Graphite reacts with numerous anhydrous metal chlorides to form inclusion compounds. Recent results on the composition and structure of these compounds and on their magnetic and catalytic properties are reported in this review.

1. Classification of Graphite Compounds

Graphite reacts with numerous elements and compounds to form graphite compounds [1a–c]. Graphite oxide, with the idealized composition $C_8O_2(OH)_2$, was the first one known and is also referred to as graphitic acid. Depending on the reaction conditions, fluorine either forms the colorless carbon monofluoride, $(CF)_x$, or a black compound, $(C_4F)_x$, containing fewer fluorine atoms. At room temperature, bromine gives bromographite, $C_{16}Br_2$, and chlorine gives the corresponding chlorine compound at low temperatures. With potassium, rubidium, and cesium, graphite forms the pyrophoric alkali-graphite compounds C_8M, $C_{24}M$, *etc.* In the presence of liquid ammonia elements such as lithium, sodium, the alkaline earth metals beryllium [2] through barium, as well as europium [2] are also capable of reacting. Oxidation of graphite in the presence of strong acids yields blue graphite salts, such as graphite hydrogen sulfate, $C_{24}{}^{+}HSO_4{}^{-}\cdot 2H_2SO_4$. Reactions between graphite and metal halides, especially metal chlorides, are quite numerous.

This account demonstrates the surprisingly high reactivity of graphite, and the question arises how can graphite react with so many diverse partners?

X-ray analysis of graphite compounds and the investigation of their physical properties such as conductivity, Hall effect [1b], magnetism, *etc.* have resulted in a better understanding of the composition of these compounds. According to the type of bond to the reaction partner, graphite compounds can be classified as homopolar and heteropolar.

Graphite oxide, carbon monofluoride, and tetracarbon monofluoride belong to the first group. Here the ligands are attached by atom bonds to the fourth valence of the carbon atoms of the carbon layers. Owing to the formation of sp^3-bonds in the first two of these compounds, the carbon layers of the graphite lattice cease to be planar and buckle in the same way as in hydroaromatic compounds. The compounds are no longer conducters, because the free fourth valence electrons in the carbon atoms of unaltered graphite are now occupied by localized C–O or C–F atom bonds. These compounds differ in their chemical behavior from other graphite compounds in that they are stable to water and organic solvents. Upon thermal decomposition, they form carbon compounds of low molecular weight such as CO, CO_2, or CF_4.

All other graphite compounds, frequently referred to as inclusion or intercalation compounds, have a more or less pronounced ionic character. Graphite may act either as an electron donor or as an electron acceptor. It acts as an acceptor with strongly electropositive alkali metals, the valence electrons of the metals occupying free levels in the conduction band of the graphite. The resulting compounds have polar structures: graphite$^{\ominus}M^{\oplus}$. With strong oxidizing agents, *e.g.*, when forming graphite salts, graphite acts as an electron donor, and the carbon layers acquire positive changes: graphite$^{\oplus}HSO_4{}^{\ominus}\cdot 2H_2SO_4$. The electron transfer between the reaction partner and the carbon layers affects only the concentration of the electrons in the conduction band and possibly, in the valence band below it. The carbon sheets remain unchanged. However, the vertical distance between the layers, which is 3.35 Å in the graphite lattice, increases considerably upon inclusion of the reaction partner, in some cases to more than 9 Å.

Stepwise intercalation is characteristic of the polar graphite compounds: the reaction partner can enter into every sheet cavity parallel to the base of the graphite lattice (1st stage); or, alternatively, it may occupy only every second, third, fourth, *etc.* cavity (2nd, 3rd, 4th, *etc.* stages). The regularity observed on intercalation is explained by the ionic character of the compounds, because the positively or negatively charged layers will tend to distribute themselves, as much as possible, at equal distances over the entire lattice. These compounds have a common tendency to decompose more or less completely upon contact with water. On thermal decomposition or upon reduction, they revert to graphite.

The metal chloride graphite inclusion compounds are also compounds of the polar type. It was only during the past ten years that a fairly large number of such substances has been prepared.

[1] Recent reviews on graphite compounds: [a] *W. Rüdorff*, Advances inorg. Chem. Radiochem. *1*, 224 (1959). – [b] *G. R. Hennig*, Progress inorg. Chem. *1*, 125 (1959). – [c] *R. C. Croft*, Quart. Rev. (Chem. Soc., London) *14*, 1 (1960).

[2] *W. Ostertag*, unpublished results.

2. Metal Halide/Graphite Compounds

a) General

Thiele [3] observed that, on heating with anhydrous $FeCl_3$, graphite increases in volume and finally puffs up. The first stage of an inclusion compound is formed below 300 °C; this contains a maximum of 68% $FeCl_3$. Individual $FeCl_3$ layer clusters, exactly as those present in crystalline ferric chloride, are intercalated between the carbon layers, thus increasing the interplanar distance to 9.40 Å [4]. Figure 1 is a schematic representation

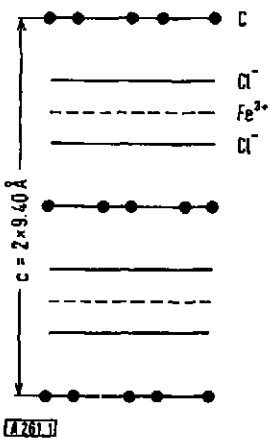

Fig. 1. Sheet layer sequence in $FeCl_3$-graphite (1st stage).

of this structure and is, in principle, also valid for most of the other metal halide/graphite compounds. *Croft* [5,6] found that numerous other metal chlorides can be intercalated in graphite. The occurrence of a reaction has also been shown for several oxychlorides and bromides. *Rüdorff* and *Zeller* [7] succeeded in obtaining $AlCl_3$-graphite compounds. A first stage compound contained 52–55% $AlCl_3$ ($1AlCl_3/9$–10 C). A 2nd and a 4th stage compound contained smaller amounts of the halide. The deep blue color of the first stage is noteworthy. The same color is displayed by the first stage of $GaCl_3$-graphite, which contains 60% $GaCl_3$ ($1\,GaCl_3$/9 C) [8].

It has been observed that not all of the chlorides that can be intercalated form the first stage compound, in which the metal chloride concentration is highest. This peculiar fact has not yet been explained. For instance, indium(III) chloride forms a second stage compound only [8], mercury(II) chloride a 3rd stage compound [9]; and with tungsten hexachloride only a 5th stage compound could be obtained [10].

A metal chloride may be included in graphite only in a chlorine atmosphere. The only exceptions seem to be $FeCl_3$, $CuCl_2$, and WCl_6. These halides, however, give off chlorine at the reaction temperature and therefore these chlorides are also intercalated in the presence of free chlorine, even though the atmosphere is primarily inert. Several other chlorides, *e.g.*, $BeCl_2$ [11], $CdCl_2$ [9], and $HgCl_2$ [9], form inclusion compounds in the presence of chlorine, despite an earlier observation [6], according to which they do not react with graphite. Table 1

Table 1. Metal chlorides inclusion of which in graphite has been demonstrated

Chlorides	Ref.	Chlorides	Ref.	Chlorides	Ref.
$BeCl_2$	[11]	$FeCl_3$	[4]	$ZrCl_4$	[6,11]
$CuCl_2$	[6,12]	$CrCl_3$	[6]	$HfCl_4$	[6]
$CdCl_2$	[9]	$RuCl_3$	[6]	$ReCl_4$	[6]
$HgCl_2$	[9]	$RhCl_3$	[6]	$PdCl_4$	[6]
$CoCl_2$	[13]	YCl_3	[6]	$PtCl_4$	[6]
$AuCl_3$	[6]	$SmCl_3$	[6]	$SbCl_5$	[6]
$AlCl_3$	[6,7]	$GdCl_3$	[6]	$TaCl_5$	[6,13]
$GaCl_3$	[6,7]	$TbCl_3$	[6]	$MoCl_5$	[6]
$InCl_3$	[6,7]	$DyCl_3$	[6]	UCl_5	[9]
$TlCl_3$	[6]	$EuCl_3$	[6]	WCl_6	[10]
				UCl_6	[9]

gives a list of halides inclusion of which in the graphite lattice has been demonstrated, albeit in many instances only qualitatively. Table 2 lists those halides for which no reaction with graphite has been observed.

Table 2. Chlorides which do not react with graphite

$MgCl_2$	$SiCl_4$	$AsCl_3$
$CaCl_2$	$GeCl_4$	$SbCl_3$
$BaCl_2$	$SnCl_4$	$BiCl_3$
$ZnCl_2$	$SnCl_2$	VCl_4
Hg_2Cl_2	$PbCl_4$	$MnCl_2$
$ScCl_3$	$PbCl_2$	$NiCl_2$
$LaCl_3$	$ThCl_4$	$PdCl_2$
$PrCl_3$	PCl_3	$PtCl_2$
$NdCl_3$	PCl_5	

Table 1 shows that intercalation is possible with chlorides of elements of the main groups as well as with those of the subgroups of the periodic table. With transition elements, only the chloride of highest oxidation state reacts as a rule (*e.g.*, $FeCl_3$, $PtCl_4$, and UCl_5, but not $FeCl_2$, $PtCl_2$, and UCl_4). Participation in an intercalation reaction is not restricted to chlorides with a certain crystal structure. Compounds that crystallize in layer lattices, *e.g.*, $FeCl_3$, $InCl_3$, and $CdCl_2$, are intercalated in the same way as compounds that form molecular lattices, *e.g.*, WCl_6. It is, however, difficult to comprehend why some chlorides can be intercalated, while this is not possible with some of their close neighbors. It is odd, for example, that $ZnCl_2$ does not react [6,9], while the chlorides of the neighboring elements, $CuCl_2$, $GaCl_3$, $CdCl_2$, and $HgCl_2$, do give intercalated compounds. The data available for rare earth chlorides are quite contradictory [6,14]. One may, for example, suspect that the conditions necessary for intercalation of $LaCl_3$, *viz.* primarily the presence of free chlorine, were not fully met in *Croft*'s experiments.

Even two metal chlorides can be intercalated in an ordered distribution. Thus, a 1st stage $CdCl_2$-$InCl_3$-graphite,

[3] *H. Thiele*, Z. anorg. allg. Chem. *207*, 340 (1932).

[4] *W. Rüdorff* and *H. Schulz*, Z. anorg. allg. Chem. *245*, 121 (1940).

[5] *R. C. Croft*, J. appl. Chem. *2*, 557 (1952).

[6] *R. C. Croft*, Nature (London) *172*, 725 (1953); Austral. J. Chem. *9*, 184 (1956).

[7] *W. Rüdorff* and *R. Zeller*, Z. anorg. allg. Chem. *279*, 182 (1955).

[8] *W. Rüdorff* and *A. Landel*, Z. anorg. allg. Chem. *293*, 327 (1958).

[9] *W. F. Siecke* Ph.D. thesis, Universität Tübingen 1958.

[10] *W. Sprießler*, Ph.D. thesis, Universität Tübingen 1960.

[11] *E. Stumpp*, unpublished results.

[12] *E. Stumpp*, Ph.D. thesis, Universität Tübingen 1960.

[13] *H. Hansmann*, Diploma thesis, Universität Tübingen 1962.

[14] *R. C. Vickey* and *N. L. Campbell*, J. Amer. chem. Soc. *79*, 5897 (1957).

containing 22.6% $CdCl_2$ and 42.4% $InCl_3$ and having a metal chloride:C ratio of 1:9.3 was obtained by heating a 2nd stage $CdCl_2$-graphite compound with $InCl_3$ in a chlorine atmosphere at 400 °C [9]. A 5th stage WCl_6-graphite compound was converted into a 1st stage $AlCl_3$-WCl_6-graphite compound by heating with aluminium chloride at 130 °C.

The metal halide/graphite compounds differ in reactivity toward water, dilute acids, or organic solvents. For example, $AlCl_3$- and $GaCl_3$-graphites are almost completely decomposed by acid, only traces of the halide remaining within the graphite. Most other intercalation compounds, however, lose only a few percent of their halide content on washing with water. Moreover, their decomposition depends on the graphite crystal size and the nature of the solvent [8]. Small crystals release a greater part of their metal halide content than large ones. From this fact, as well as from density determinations and X-ray studies, it is clear that decomposition is restricted to the peripheral regions of the crystals. The solvent attacks the crystals at the edges of the layers and dissolves out the metal halide that is intercalated there. As soon as the metal halide content of the periphery of the crystal is reduced, the layer spacing shrinks back to that of graphite. The crystals then consist of a thin outer shell of graphite protecting the undecomposed inclusion compound in the inner regions from further attack.

b) The Function of the Chlorine during Intercalation

The presence of chlorine is required in all the reactions between graphite and metal chlorides that have been investigated so far. Chlorine does not act as a catalyst, as was assumed earlier; a certain amount is always included with the metal chloride [15]. In $AlCl_3$- and $GaCl_3$-graphite, the additional chlorine is incorporated at a ratio of one Cl per three MCl_3.

Dzurus and *Hennig* [15] conclude from the increase in electrical conductivity of graphite upon incorporation of small amounts of $AlCl_3$ and from the sign of the Hall constant that the additional chlorine abstracts electrons from the graphite. Graphite thereby becomes a p-type conductor and the carbon layers acquire positive charges. The ionic nature of these compounds can be represented by the formulae $[C_n]^{\oplus}_{graphite}\ Cl^{\ominus}\cdot 3MCl_3$ or $[C_n]^{\oplus}_{graphite}\ [MCl_4]^{\ominus}\cdot 2MCl_3$, where n is approximately 27 for the 1st stage. Since chlorine acts as an electron acceptor, the compounds may be considered as graphite chloride stabilized by the intercalation of $AlCl_3$ or $GaCl_3$. Formulation as a chloro-complex enables us to recognize the close relationship to the graphite salts, for example, to the 1st stage of the graphite bisulfate $C_{24}{}^{\oplus}HSO_4{}^{\ominus}\cdot 2H_2SO_4$. The $AlCl_3$- and $GaCl_3$-compounds are the only metal halide/graphite compounds known which have blue colors similar to that of the bisulfate. One is tempted to conclude that the blue color is somehow associated with a concentration ratio of acceptor atoms to carbon atoms in the range of 1:24 to 1:27 [16].

In all the other metal chloride/graphite compounds investigated so far, the quantity of chlorine additionally bound is considerably smaller than in the $AlCl_3$ or the $GaCl_3$-graphite compound and apparently changes with the reaction conditions. Analysis is made difficult by the fact that, on heating in a chlorine atmosphere, the graphite takes up 0.5–1.0% chlorine, which is not released *in vacuo* at room temperature. So far, the highest chlorine content has been found in preparations of $HgCl_2$-graphite and $CoCl_2$-graphite, which have approximately 1Cl/6 MCl_2. Similar values for the ratio of chlorine: metal chloride were obtained by *Dzurus* and *Hennig* [17] during studies of $InCl_3$- and $CdCl_2$-graphite. There were significant differences in chlorine content, depending on whether the compounds were prepared from natural or synthetic graphite. It was shown from conductivity measurements that here, too, the acceptor concentration is approximately equal to the quantity of additionally bound chlorine. It is therefore reasonable to assume that these compounds also have ionic character. Their composition can then be represented by the idealized formula: graphite$^{\oplus}[HgCl_3]^{\ominus}\cdot 5HgCl_2$ or graphite$^{\oplus}[InCl_4]^{\ominus}\cdot 5InCl_3$, *etc.*

So far, acceptor concentrations calculated from conductivity measurements are valid only for samples that are low in metal chloride (metal chloride: C-atoms = 1:135 to 1:185). It has as yet not been established whether these results can be extended to the homogenous 1st and 2nd stages, where metal chloride concentrations are 10 to 20 times higher. If the formulation presented here for the composition of these compounds is correct, it remains unresolved why the intercalation of $AlCl_3$ and $GaCl_3$ should result in an acceptor concentration which is twice as high as that for all the other metal chlorides which undergo this reaction. Since the intercalation reaction is restricted to a few chlorides, one may perhaps conclude, that what takes place is a specific interaction between the chloride and the carbon layers or their electrons. The questions of the nature of this interaction and whether it is in any way induced by the acceptor effect of the additionally bound chlorine remain to be answered by further studies.

c) $CuCl_2$-, $CdCl_2$-, $HgCl_2$-, $CoCl_2$-, UCl_5- and WCl_6-Graphite

These compounds have been extensively investigated in recent times. They are prepared by standard methods [7,8]. Table 3 shows the optimum temperatures for the intercalation reaction and the composition of the stages richest in halides. The data refer to preparations made from finely divided flocculent graphite (from Kropfmühl near Passau, Germany) with an ash content lower than 0.1%.

While the reaction of $CuCl_2$ with graphite proceeds even on heating in a nitrogen atmosphere, preparations with a Cu:Cl

[15] *M. Dzurus* and *G. R. Hennig*, J. Amer. chem. Soc. *79*, 1051 (1957).

[16] Among the alkali-graphite compounds the second stage, $C_{24}M$(M = K, Rb, and Cs), is also deep blue, the first stage C_8M is bronze-colored, and the stages which contain less alkali are distinctly black. It must be conceded that in such cases the carbon layers serve as electron acceptors. Nevertheless, it is remarkable that a blue color appears even with these compounds, provided they have a 1:24 ratio of acceptor atom to carbon atoms.

[17] *M. L. Dzurus* and *G. R. Hennig*, personal communication.

Table 3. Composition of some metal chloride/graphite compounds

	$CuCl_2$	$CdCl_2$	$HgCl_2$	$CoCl_2$	WCl_6	UCl_5
Reaction temperature [°C]	400	490	250	430	300	420
Maximum metal chloride content [%]	69.6	57.8	50	64.3	32	48
Ratio metal chloride: C atoms	1:4.9	1:11.1	1:20	1:5.6	1:70	1:37
Stage	1	1	3	1	5	2

ratio of 1:1.7 are always obtained. This means that Cu(I) can be intercalated together with Cu(II). To form a homogeneous 1st stage of $CuCl_2$-graphite, the reactant must be heated at 400 °C for eight days in a chlorine atmosphere. The low rate of reaction between the graphite and $CuCl_2$ seems to indicate that only the gas phase halogen is involved, since the vapor pressure of $CuCl_2$ at 400 °C is still relatively low. A second and fourth stage compound have been demonstrated in addition to the first stage product.

Tungsten hexachloride reacts with graphite in a nitrogen atmosphere to form an intercalation compound containing W(VI) and W(V). Products containing exclusively hexavalent tungsten begin to appear only when the reaction occurs in a chlorine atmosphere.

No reaction between graphite and $CdCl_2$, $HgCl_2$, $CoCl_2$, or UCl_5 has been observed in nitrogen or hydrogen chloride atmospheres. The preparation of the first stage of $CdCl_2$-graphite in the presence of chlorine requires very long reaction times (up to seven days). Heating for 15 hours at 540 °C yields the second stage compound which contains 37% $CdCl_2$.

The data in Table 3 show the great differences in behavior of the various chlorides towards graphite. Copper(II) chloride can be intercalated in ratios of up to $1CuCl_2$:5C atoms to yield a first stage compound, while the tungsten hexachloride inclusion compound is formed in a ratio of only 1 WCl_6:70 C atoms, producing a fifth stage product. It is not yet known what causes these differences.

3. Structure of Metal Chloride/Graphite Compounds

So far, a complete structural analysis has been made only for first stage $FeCl_3$-graphite [4,18]. The Fe^{3+} ions located in the center between the carbon layers (Fig. 1) form the same hexagonal network, with almost identical Fe–Fe distances, as occurs in crystalline $FeCl_3$. Because of the varying dimensions of the two networks, the Fe^{3+} ions are not preferentially oriented toward individual carbon atoms. The distance between the carbon planes and the neighboring chloride ion layers is 3.36 Å. The chloride ion layers are distorted, because about half of the chloride ions assume positions with a recognizable coordination to the carbon atoms in the neighboring graphite sheets.

With the other metal chloride inclusion compounds, so far, only the arrangement of the carbon layers and a rise in the interplanar distance caused by the intercalated metal chloride have been demonstrated with any degree of certainty. The orientation of the carbon planes is always identical with that of the hexagonal graphite modification, *i.e.*, ABAB....

This is all the more remarkable, because in alkali-graphite compounds and graphite salts, intercalation entails a shift of the carbon planes in a direction parallel to the base of the crystal.

The intercalated chloride increases the vertical distance between the carbon layers (in the direction of the c-axis) to 9.4–9.7 Å. (Table 4). There are good reasons that the vertical distances for the various chlorides vary so little. The structure of the compound is always such that the metal ion is at the midpoint between the carbon planes while the chloride ions are next to the carbons. It is essentially the close-packed chloride ions that determine the bulk of the intercalated halides in the direction of the c-axis.

Table 4. Vertical distances between the carbon layers in intercalated metal chloride/graphite compounds

Halide	Distance between layers [Å]	Stage
$CuCl_2$	9.40	1
$FeCl_3$	9,40	1
$InCl_3$	9,48	2
$CoCl_2$	9,50	1
$CdCl_2$	9,51	1
$AlCl_3$	9,54	1
$GaCl_3$	9,56	1
WCl_6	9,62	5
UCl_5	9,68	2
$HgCl_2$	9,78	3

The powder pattern of several intercalation compounds shows interferences which cannot be attributed to the arrangement of the carbon lattices. These interferences allow a few conclusions with regard to the structure of the intercalated halide layers. Thus, the spatial arrangement of the In^{3+} ions in the $InCl_3$-graphite are the same as in crystalline indium chloride [19]. Five (h00) or (hk0) interferences appear in the patterns of WCl_6-graphite. These can be indexed hexagonally with a = 6.14 Å. Since WCl_6 forms a hexagonal molecular lattice with a = 6.10 Å [20], the agreement in lattice constants indicates identical symmetries. This leads us to believe that the arrangement of WCl_6 molecules in the intercalation compound is identical with that in the hexagonal base plane of crystalline WCl_6. However, the regularity of orientation of WCl_6 layers towards each other disappears. This is understandable, since five carbon layers are now located between them.

Intercalated $CuCl_2$ forms $CuCl_2$-chains identical with those present in the lattice of the crystalline chloride. In the inclusion compound, the chains are evidently oriented towards each other much like those in the a-b plane of $CuCl_2$-crystals.

The maximum MCl_x:C ratio obtainable for an intercalation compound may be calculated from the bulk of the carbon atom in the graphite lattice and from the dimensions of the halide lattice in the base plane, provided the latter is known. So far, however, this maximum ratio has not been attained in any compound. At the best, the metal chloride layers were approximately 85% filled. This means that the intercalated layers have a considerable number of gaps.

[18] *J. M. Cowley* and *J. A. Ibers*, Acta crystallogr. (Copenhagen) *9*, 421 (1956).

[19] *D. H. Templeton*, J. physic. Chem. *58*, 940 (1954).

[20] *J. A. A. Ketelaar* and *G. W. Oosterhout*, Rec. Trav. chim. Pays-Bas *62*, 197 (1943).

4. Magnetic Properties of the Compounds

a) Inclusion Compounds Containing Diamagnetic Chlorides

Graphite shows an abnormal, *i.e.* very high, diamagnetism in the direction of its hexagonal axis (perpendicular to the carbon layers). This must be attributed to the specific π-electron distribution in the lattice [21,22]. This diamagnetism is extremely sensitive to disturbances such as those caused, for example, by the inclusion of foreign atoms [23]. It is, therefore, to be expected that this abnormal diamagnetism would change (or possibly even disappear) upon formation of graphite intercalation compounds. This disappearance of abnormal diamagnetism has already been proved with alkali-graphite compounds [24] and bromographite [25-27]. No data are as yet available for the metal chloride compounds. Since the diamagnetism of graphite in these substances yields information about their composition (see Section 4b), we investigated intercalation compounds with diamagnetic chlorides first. The diamagnetism of graphite was calculated from the magnetic susceptibilities, subtracting the diamagnetic value of the metal chloride. We assumed that the diamagnetism of the free and intercalated metal chloride is identical.

Table 5. Molar susceptibilities $\chi_{mol} \times 10^{-6}$ [cm³/g] of $AlCl_3$-, $GaCl_3$-, $InCl_3$-, and $CdCl_2$-graphites and the graphite increments calculated therefrom (both referred to 1 gram atom of carbon)

Compound	Stage	$\chi_{Mol} \cdot 10^6$ at 293 °K	195 °K	78 °K
$C(AlCl_{3,2})_{0,099}$	1	−10,9	−9,3	−10,4
Graphite increment		−5	−3	−4
$C(AlCl_{3,3})_{0,063}$	2	−10,3	−9,4	–
Graphite increment		−6	−5	–
$C(AlCl_{3,3})_{0,025}$	4	−11,6	−12,2	−22,7
Graphite increment		−10	−11	−21
$C(GaCl_{3,2})_{0,101}$	1	−14,1	−13,5	−12,8
Graphite increment		−6	−5	−4
$C(GaCl_{3,3})_{0,049}$	2	−10,2	−9,5	−9,9
Graphite increment		−6	−5	−6
$C(GaCl_{3,2})_{0,033}$	4	−12,3	−13,2	−18,0
Graphite increment		−10	−10	−15
$C(InCl_3)_{0,059}$	2	−13,3	−13,3	–
Graphite increment		−8	−8	–
$C(CdCl_2)_{0,142}$	1	−15,5	−16,3	−14,8
Graphite increment		−7	−7	−6
$C(CdCl_2)_{0,081}$	2	−13,4	−13,7	−11,5
Graphite increment		−8	−9	−6

Table 5 shows the composition of the compounds and their molar susceptibilities. The small amounts of chlorine bound additionally in the intercalation compounds containing $InCl_3$ and $CdCl_2$ have been neglected. Their effect on the calculation is insignificant.

The main result of these measurements is the fact that the abnormal diamagnetism of pure graphite is no longer present in the 1st and 2nd stages of the metal chloride intercalation compounds. An average susceptibility of -6×10^{-6} cm³/g per gram atom of carbon was found. Incidentally, the same value is obtained for the susceptibility of graphite in bromographite, when the data of *Ubbelohde* et al. [27] are considered in an analogous manner. Thus, intercalation of a metal chloride or bromine reduces the susceptibility of graphite to the value found for the carbon present in diamond and in aliphatic compounds.

The susceptibilities of graphite in the two fourth stages are higher than in the first and second stage; they increase even further at the lowest measuring temperature (78 °K). Thus, the abnormal diamagnetism of the graphite is still evident to a slight degree in the fourth stage compound. However, even the values for the 4th stage are low in comparison with pure graphite and indicate that a change in the electron status has taken place throughout the entire lattice, despite the fact that a metal chloride inclusion is present in only one out of every four interlaminar cavities of the graphite lattice.

b) Inclusion Compounds Containing Chlorides of the Transition Elements

The data obtained with the four compounds containing intercalated diamagnetic halides may be generalized, and hence the assumption can be made that the abnormal diamagnetism of graphite no longer occurs in those other metal chloride/graphite compounds which form a first and a second stage substance. This generalization leads to a method for evaluating the degree of oxidation of intercalated metal cations of halides of the transition elements from measurements of the magnetism of the inclusion compound.

According to *Hennig* [28], some of the metal cations in the inclusion compounds of halides of the transition elements act as electron acceptors towards graphite, thereby acquiring a lower degree of oxidation. The composition of, for instance, $FeCl_3$-graphite would then correspond to the formula graphite$^{\oplus}$ $[Fe^{2+}Cl_3]^{\ominus} \cdot 2\text{–}3\ FeCl_3$. Magnetic measurements on $FeCl_3$-graphite [4] have shown that the susceptibility of the intercalated $FeCl_3$ is somewhat lower than that of free $FeCl_3$. This has been attributed to a change of the Weiss constant in the Curie-Weiss equation. However, the values of the moments of Fe^{2+} and Fe^{3+} ions are not very far apart. Thus, the measurements cannot supply the answer to the question whether $^1/_3$ or $^1/_4$ of the intercalated ferric chloride is reduced to Fe(II), as shown by the above formulation.

We have investigated $CuCl_2$-graphite [12] and WCl_6-graphite [10]. The Cu^{2+} ion is paramagnetic, while the Cu^+ ion is diamagnetic. If the $CuCl_2$-graphite could be formulated as graphite$^{\oplus}[Cu^{\oplus}Cl_2]^{\ominus} \cdot 2CuCl_2$ (with mono-

[21] *N. Ganguli* and *K. S. Krishman*, Proc. Roy. Soc. (London) *177*, 168 (1940).

[22] *R. Smolukowski*, Rev. mod. Physics *25*, 178 (1953).

[23] *W. Klemm:* Magnetochemie. Akademische Verlagsgesellschaft, Leipzig 1936, p. 222.

[24] *W. Rüdorff* and *E. Schulze*, Z. anorg. allg. Chem. *277*, 156 (1954).

[25] *R. Juza*, *H. Lübbe*, and *L. Heinlein*, Z. anorg. allg. Chem. *258*, 105 (1949).

[26] *M. Goldsmith*, J. chem. Physics *18*, 523 (1950).

[27] *F. R. M. McDonnel*, *R. C. Pink*, and *A. R. Ubbelohde*, J. chem. Soc. (London) *1951*, 191.

[28] *G. R. Hennig:* Proceedings 1st and 2nd Conference on Carbon. University of Buffalo 1956, p. 103.

and divalent copper) then a considerable decrease in the susceptibility of the intercalated copper chloride would be expected. The situation is reversed in the case of WCl_6: this compound is diamagnetic, while the pentavalent tungsten in WCl_5, which has one unpaired electron, shows temperature-dependent paramagnetism [29]. The structure graphite$^{\oplus}$ $[W^{5\oplus}Cl_6]^{\ominus}\cdot 2WCl_6$ would also imply temperature-dependent paramagnetism for the intercalated tungsten chloride.

The measurements were made on a first stage $CuCl_2$-graphite, containing 69.6% $CuCl_2$, and on a first stage $AlCl_3$–WCl_6-graphite, containing 28.1% WCl_6. Measurement of a graphite compound containing exclusively WCl_6 was omitted, since it exists only as a fifth stage substance and the diamagnetism of graphite cannot be calculated with certainty in such a case. To calculate the molar susceptibility of the intercalated halide, the data were corrected for diamagnetism in the usual manner. The contribution of graphite, *viz.* -6×10^{-6} cm³/g per gram atom, was taken into account according to the discussion in Section 4a.

The results are shown in Table 6: the susceptibility of intercalated $CuCl_2$ is dependent on the temperature in a somewhat different fashion and is somewhat lower

Table 6. Molar susceptibilities $\chi_{mol}\times10^6$ [cm³/g] of $CuCl_2$ and WCl_6 in the free crystalline state and intercalated in graphite

	78 °K	195 °K	293 °K	443 °K
$CuCl_2$ crystalline $\Theta = 80$ °K	2558	1863	1377	1035
$CuCl_2$ intercalated $\Theta = 72$ °K	2748	1843	1330	981
WCl_6, crystalline	−75,4	−75,4	−75,4	
WCl_6, intercalated		−92	−92	

above 195 °K than the susceptibility of pure, crystalline $CuCl_2$. The deviations can, however, be explained by a modified crystal field in the intercalated state and the influence of this field on the orbital contribution to the magnetic moment. The decrease in susceptibility at room temperature is 3.4%. This places it just beyond the limit of the method of error, which is approximately 2%. The presence of Cu(I) should manifest itself by a much more pronounced decrease of the susceptibility. Assuming that only every tenth intercalated Cu^{2+} ion is reduced, the susceptibility should have decreased to approximately 1220×10^{-6} cm³/g, *i.e.* it should have been reduced by 11.4%. A value of only 900×10^{-6} cm³/g would be expected from the above given formulation, where $^1/_3$ of the intercalated copper is present as Cu(I). Intercalated WCl_6 shows temperature-independent diamagnetism that is even higher than the value for free WCl_6. The presence of paramagnetic W^{5+} ions can therefore be excluded with certainty.

Thus, measurements of the magnetism show that the cations of the intercalated metal chlorides do not function as electron acceptors in these two compounds. It is most likely that in this case, too, the small quantity of chlorine additionally bound is responsible for the occurence of intercalation.

[29] *W. Klemm* and *H. Zocher*, Z. anorg. allg. Chem. *227*, 201 (1936.).

5. Catalytic Properties

Very little is known so far about the catalytic properties of metal chloride/graphite compounds. Study of these may, however, become of interest, since it is possible that inclusion of certain halides in graphite may produce selective catalysts.

The first such study dealt with the catalytic formation of hydrogen bromide from its elements on graphite and two intercalation compounds, namely $CdCl_2$- and $InCl_3$-graphite [30]. These compounds were chosen because of their thermal stability and their resistance to attack by the reagents. The heat of activation was chosen as a measure of the change in catalytic properties induced by intercalation of a halide. The activation energy for the homogeneous HBr-formation, according to *Bodenstein* [31], is 41 kcal/mole. With graphite as catalyst, a value of only 12–13 kcal/mole has been obtained. This is in good agreement with the data of *Schwab* and *Lober* [32], who obtained a heat of activation on activated charcoal of 15 kcal/mole. The heat of activation was considerably higher with either one of the metal chloride intercalation compounds as catalyst. We measured 26 kcal/mole for $InCl_3$-graphite (second stage) and 30 kcal/mole for $CdCl_2$-graphite (first stage).

The increase in the heat of activation caused by intercalation can be explained by the structure of the inclusion compounds. It is known that during the catalytic formation of hydrogen bromide on carbon, the bromine molecules are adsorbed on the surface of the catalyst and are thereby activated. Several observations indicate that the adsorption of bromine molecules takes place at the base plane of the graphite crystal [33–35]. At the very least, there is a tendency for preferential adsorbtion at that plane. The activation of bromine may be pictured as follows. The bromine molecules attract electrons from the conduction band of the graphite and thus become polarized to $Br_2^{\ominus}$. However, the polarization does not have to proceed so far that electrons become part of the chemisorbed molecules. In the intercalation compounds, the shift of the π-electrons toward the adsorbed Br_2-molecules is more difficult, hence, the heat of activation increases. The additionally bound chlorine itself acts as electron acceptor and thus decreases the electron density in the conduction band.

This concept implies that a reaction in which electrons are transferred from the chemisorbed molecules to the catalyst, *i.e.* a donor reaction, should proceed better on a metal chloride inclusion compound than on graphite. This is indeed so, as has been demonstrated by recent investigations on dehydrogenation of formic acid [11].

[30] *E. Stumpp* and *W. Rüdorff*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. (1962), *66*, 648 (1962).

[31] *M. Bodenstein* and *S. Lind*, Z. physik. Chem. *57*, 168 (1907).

[32] *G.-M. Schwab* and *F. Lober*, Z. physik. Chem. Abt. A *186*, 321 (1940).

[33] *W. Rüdorff*, Z. anorg. allg. Chem. *245*, 383 (1940).

[34] *U. Hofmann* and *W. Höper*, Naturwissenschaften *32*, 225 (1944).

[35] *G. Ruess* and *F. Vogt*, Mh. Chem. *78*, 222 (1948).

Finally, attention should be called to the possibility of catalyzing reactions of graphite itself by intercalation of metal chlorides. An example of this is the reaction

$$4\,HCl + O_2 \rightarrow 2\,Cl_2 + 2\,H_2O$$

on a $CuCl_2$-graphite catalyst, where vigorous combustion of the graphite occurs, even at 425 °C and where phosgene is formed besides the chlorine. On the other hand, pure graphite is still not noticeably attacked by an HCl/air mixture at this temperature. Other intercalated metal chlorides, such as $CoCl_2$ or WCl_6, also catalyze the combustion of graphite. It is probable that the reaction between graphite and chlorine is also catalyzed by intercalated metal chlorides. According to *Dzurus* and *Hennig* [17], the consumption of chlorine during intercalation of a metal chloride is considerably higher than that indicated by the quantity intercalated in the lattice.

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The Silicate Bond from the Standpoint of Electronic Theory [*]

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Dedicated to Prof. Dr. Ulrich Hofmann on the occasion of his 60th birthday

Starting from a consideration of the "undisturbed" Si–O–Si bond in the modifications of silicic acid, the types of bonds present in silicates with polymeric Si–O–Si groups are discussed, taking into consideration the inductive effect of the metal cations. Experimental data on the influence of various substituents in organopolysiloxanes form the basis for this discussion. The bonds in silicates differ by direction and character and are determined by the relative ability of the metal atoms to act as donors and by the degree of condensation of the Si–O–Si bond. It is shown that on this basis, it is possible to explain, for example, why silicates differ in their atomic distances, susceptibility to cleavage by acids, stability relationships, and other properties.

Introduction

The building unit of the silicates with polymeric anions, the Si–O–Si (siloxane) bond, is also the basic skeleton of the organopolysiloxanes. Thus, the interesting situation results that the same configuration of atoms can be studied, under various conditions and combinations, in both crystals and molecules. It has already been shown that detailed discussion of the existing data was able to disclose general regularities with respect to structural relationships [1]. These considerations are extended in the following pages to the problem of the silicate bond.

In organopolysiloxanes, the Si–O–Si bond – judging by its reactivity – is not nearly so stable as might be assumed from the standpoint of silicate chemistry. It can be cleaved by bases, protic acids, Lewis acids, and organometallic compounds, such as Grignard reagents [2] or organoaluminum compounds [3]. However, no sharp differences should exist between the reactivity of the Si–O–Si bonds in silicic acids and silicates on the one hand, and in methylpolysiloxanes on the other; silicic acids and silicates appear to react more slowly, since at lower temperatures, they are decomposed in nearly all degradations via surface boundary reactions while methylpolysiloxanes usually react in homogeneous phase.

The study of the influence exerted by substituents on the reactivity and the physical constants of the Si–O–Si bond in organopolysiloxanes is important to our understanding of the types of bonds present. The results can be reconciled with the electron donor or electron acceptor properties of the substituents, and can be interpreted as inductive effects.

Consequently, a valuable basis for the discussion of the silicate bond is available, for even in silicates, the nature of the Si–O–Si bond must be influenced by the inductive effects of metal cations. This influence increases with the difference in electronegativity between the metal and the silicon and with the number of metal cations present in the lattice. Because of this, the former practice of concentrating on orthosilicates for purposes of investigation of the Si–O bond seems undesirable. The "undisturbed" character of the bond can hold only in those modifications of SiO_2 that contain exclusively Si–O–Si bonds. These modifications are therefore taken as the starting point for this discussion.

[*] Presented as a plenary lecture at the 39th Annual Meeting of the Deutsche Mineralogische Gesellschaft (German Mineralogical Society) in Tübingen on Sept. 13th, 1961. Abstract: Fortschr. Mineralog. *39*, 354 (1961).

[1] *W. Noll*, Naturwissenschaften *49*, 505 (1962).

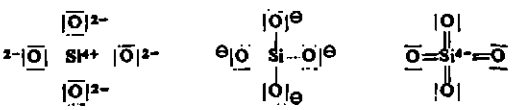
[2] *H. Kautsky*, German Patent Application 1028 784 (June 25th, 1955).

[3] *R. C. Anderson* and *G. J. Sleddon*, German Patent Application 1094261 (Sept. 28th, 1957) ICI.

[4] *L. Pauling:* The Nature of the Chemical Bond. 2nd Edit., Cornell University Press, Ithaca, N.Y. 1948.

Bonds in SiO_2 Networks

The concept developed by *Pauling* [4] that the Si–O bond corresponds to a resonance structure involving the participation of a covalent (σ-) limiting structure *(1)* and a polar limiting structure *(2)*, was held valid for a long time. It could be calculated from the difference in electronegativity between silicon and oxygen that each limiting bond form contributes approximately 50% of the total.



Limiting forms of the bond in the SiO_4 complex

(1) polar form *(2)* covalent form *(3)* double bond form

On this basis, the fact that the Si–O nuclear distance is shortened both in comparison with either the sum of the atomic radii or the sum of the ionic radii could be readily understood. This distance is 1.60 Å (Table 1) in the lattices of the various modifications of SiO_2, and should be discussed separately from the Si–O distance in silicates [5].

Table 1. Si–O distances [Å] in various modifications of SiO_2

Modification	Individual values	Average value
Low quartz [7]	1.61; 1.62; 1.60; 1.62	1.615
[8]	1.605	1.605
High quartz [9]	1.61_2	1.61_2
Low cristobalite [10]	1.59; 1.59	1.59
Keatite [11]	1.58; 1.59; 1.61; 1.61; 1.61; 1.61; 1.57; 1.57	1.59_4
Coesite [12]	1.60; 1.63; 1.61; 1.61; 1.62; 1.60; 1.62; 1.61	1.61_5
SiO_2 glass [13]	1.60 ± 0.05	1.60

According to *Schomaker* and *Stevenson* [14], a Si–O nuclear distance of 1.67 Å is obtained on the assumption that the bond is a covalent-polar resonance bond, with equal contributions from the two limiting resonance structures. Even though this is smaller than the sum of the ionic and the atomic radii, it is greater than the experimental value (Table 2).

Better agreement with the experimental data is obtained by assuming that, in addition, a contribution is made by a d_π–p_π double bond form [6]. The contribution of this form can be evaluated, among other things, from the following considerations. The formal charge on the Si atom differs in the three limiting forms *(1)* to *(3)*. It amounts to 4^+ in the polar form, 0 in the covalent form, and 4^- in the double-bond form. A resonance bond consisting of the polar and covalent limiting forms in a 1:1 ratio would lead to a formal charge of 2^+ on the Si atom, and is therefore not very probable. By incorporating the double-bond form, the formal charge on the Si atom can be reduced. It becomes zero when three limiting forms make equal contributions to the formation of the bond. Using this hypothesis, *Pauling* calculated a Si–O distance of 1.63 Å, which comes very close to the experimental value for the modifications of SiO_2 (1.60 Å) [Table 2].

Table 2. Experimental and calculated Si–O nuclear distance [Å]

	Experimental	Calculated			
		sum of the ionic radii	sum of the atomic radii	resonance bond (covalent-polar)	resonance bond (covalent-polar-double bond)
Modifications of SiO_2	1.60 [15]	1.71	1.83	1.67	1.63
Methylpolysiloxanes	1.64 [16]				

A resonance bond of this type also may be used to explain the value of the valence angle of the Si–O–Si bond. The valence angle for oxygen in siloxanes has a pronounced tendency to stabilize at 130–140° [17]. This value is quite large in comparison to other X–O–X valence angles (H–O–H: 105°, C–O–C: 110°). The non-directional polar bond constituent makes no contribution to the stabilization of this large angle. With a pure σ-bond, an angle of 90° would be expected, and with a pure double bond an angle of 180°. Actually, the angle found experimentally is approximately the arithmetic mean of the two values.

Influence of Substituents in Organopolysiloxanes

The two structures shown in Scheme 1 are possible depending on whether the hydrocarbon radicals in organopolysiloxanes act as electron donors or electron acceptors.

Effects of this type can be observed in infrared and Raman spectra. Thus, on stepwise substitution of methyl groups by chlorine atoms [18] in hexamethyl-

[5] Pauling treated the Si–O bond using the isolated SiO_4 complex as an example, but called attention to the fact that, in silicate lattices, the effect of the metal atoms on the Si–O bond must be taken into consideration [6].

[6] *L. Pauling*, J. physic. Chem. *56*, 361 (1952).

[7] *P. H. Wei*, Z. Kristallogr. *92*, 355 (1935).

[8] *F. Machatschki*, Z. Kristallogr. *94*, 222 (1936).

[9] *J. V. Smith*, Acta crystallogr. *7*, 479 (1954).

[10] *W. Nieuwenkamp*, Z. Kristallogr. *92*, 82 (1935).

[11] *J. Shropshire, P. P. Keat*, and *Ph. A. Vaughan*, Z. Kristallogr. *112*, 409 (1959).

[12] *T. Zoltai* and *M. J. Buerger*, Z. Kristallogr. *111*, 129 (1959).

[13] *J. Zarzycki*, Verres et Réfractaires *11*, 3 (1957).

[14] *V. Schomaker* and *D. P. Stevenson*, J. Amer. chem. Soc. *63*, 37 (1941).

[15] See Table 1. [16] See Table 4.

[17] *W. Noll*, Fortschr. Mineralog. *34*, 63 (1956).

[18] *G. K. Scholl*, Ph.D. Thesis, Technische Hochschule Stuttgart, 1959.

disiloxane (Table 3), a strong shift of the symmetric Si–O–Si vibration toward higher frequencies is found. The frequency of this vibration lies at 523 cm^{-1} for

Si–O–Si bond weakened
Si–C bond strengthened

R = Electron donor

Si–O–Si bond strengthened
Si–C bond weakened

R = Electron acceptor

Scheme 1 Influence of the substituents in organopolysiloxanes on the strength of the Si–O–Si bond

hexamethyldisiloxane, and reaches 722 cm^{-1} for hexachlorodisiloxane. Similarly, the asymmetric Si–O–Si vibration is clearly shifted toward higher frequencies, even though not to the same extent; it shifts, in fact, from 1050 cm^{-1} for hexamethyldisiloxane to 1110 cm^{-1} for hexachlorodisiloxane.

In discussing this effect, it must be noted that these changes in frequency can be caused both by alteration of the force constant, *i.e.* by strengthening or weakening of the bond, and by alterations in the mass and in the valence angle. Calculations on a simple three-mass model show qualitatively that strengthening of the bond (increase in the force constant) leads to increases in the frequencies of the asymmetric and symmetric Si–O–Si vibrations, while any increase in the mass leads to a decrease in the frequencies. An increase in the angle lowers the frequency of the symmetric, and increases the frequency of the asymmetric Si–O–Si vibration. The increase in frequency observed for both vibrations must therefore be caused by a great increase in the force constant, which overcompensates the opposite effect of the increase in mass. Similarly, the influence of a contingent increase in the angle is masked by that of the force constant, as the increase in frequency of the symmetric vibration shows.

If the methyl groups are partially replaced by halogenomethyl groups [19], the frequency of the asymmetric Si–O–Si vibration again increases (Table 3); however, this increase is relatively unimportant. No significant differences between chloro- and bromo-substituted compounds can be observed. The frequency of the symmetric Si–O–Si vibration, on the contrary, remains unaltered in the case of chloro-substituted compounds, and is even shifted to somewhat lower values in the case of bromo-substitution.

These results may be explained in the following way: Since the halogen atoms are not attached directly to the silicon atom, their influence on the Si–O–Si bond is not so great. On the other hand, the influence of the increase in mass – and of a contingent increase in angle – becomes more important. This is shown in the spectra by the fact that ν_{as} increases only slightly on substitution by chlorine; with regard to the symmetric vibration, the effects of the strengthening of the bond, on the one hand, and the increase in the mass and the angle, on the other hand, compensate each other. With the bromo-substituted products, the influence of the increase in mass predominates, so that here the symmetric Si–O–Si vibration lies at somewhat lower frequencies.

The alterations in the infrared and Raman frequencies of the Si–O–Si vibration on replacement of the methyl groups by phenyl, hydroxyl, or hydrogen can be interpreted in the same way [20] (Table 3). In all cases, the substituent acts as an electron acceptor and strengthens the Si–O–Si bond, as is shown by increases in the frequencies of ν_s and ν_{as}. It is also interesting that a hydrogen substituted on silicon also exerts this effect; this agrees with the chemical fact that the Si–H bond has a hydride-like behavior.

The extent to which the Si–O–Si valence angle is altered during these substitutions is shown by electron diffraction studies on the vapor or by X-ray diffraction studies of the crystal lattice. Table 4 shows that this angle lies with remarkable constancy between 130 and 140°. In hexahydrogendisiloxane, the valence angle is reported to be 142 ± 4°, and in hexachlorodisiloxane, 175 ± 5°; however, both values have not yet been thoroughly checked experimentally. The variation in these values is in complete agreement with theory, and can be explained as an expression of the increase in the contribution of a d_π–p_π bond form to the Si–O–Si bond under the influence of the weakly (H) and strongly (Cl) electronegative substituents.

Table 3. Infrared and Raman frequencies of the Si–O–Si bond [cm^{-1}]
L = in solution, S = undiluted.

Siloxane	ν_{as} Infrared	ν_s Infrared	ν_s Raman
$(CH_3)_3SiOSi(CH_3)_3$	1050 (L) [21]	523 (S) [21]	
	1055 (S) [22]	522 (S) [22]	519 (S) [22]
$Cl(CH_3)_2SiOSi(CH_3)_2Cl$	1070 (S,L) [20]	578 (S,L) [20]	579 (S) [20]
$Cl_2(CH_3)SiOSi(CH_3)Cl_2$	1085 (L) [18]	638 (L) [18]	634 (S) [18]
$Cl_3SiOSiCl_3$	1110 (L) [18]		722 (S) [18]
$[ClCH_2(CH_3)_2Si]_2O$	1069 (L) [21]	521 (S) [21]	
$ClCH_2(CH_3)_2SiOSi(CH_3)_3$	1064 (L) [21]	521 (S) [21]	
$[BrCH_2(CH_3)_2Si]_2O$	1069 (L) [21]	513 (S) [21]	
$BrCH_2(CH_3)_2SiOSi(CH_3)_3$	1063 (L) [21]	515 (S) [21]	
$[(C_6H_5)(CH_3)_2Si]_2O$	1063 (L,S) [20]	560 (L,S) [20]	562 (S) [20]
$[H(CH_3)_2Si]_2O$	1058 (L,S) [20]	550 (L,S) [20]	550 (S) [20]
$[HO(CH_3)_2Si]_2O$	1073 (L) [20]	555 (L) [20]	554 (L) [20]

The nuclear distances are affected by the strengthening of the bond on replacement of CH_3 by H or Cl (Table 4) to such a small extent that the deviations approach the limit of error of the measurements. The average value for the Si–O nuclear distance in methylpolysiloxanes (1.64) differs from the corresponding value for the modifications of SiO_2 (1.60) in the expected direction; an effect of the higher polarity of the Si–O bond by the electron-donor substituents can be used as an explanation for the increase in the distance on replacement of oxygen by methyl groups.

The inductive effect of the substituents can be seen most clearly from the chemical behavior of the siloxanes. An especially sensitive index for discerning fine distinctions in the nature of the siloxane bond is its behavior

[19] *W. Simmler*, Angew. Chem. *73*, 761 (1961).

[20] *H. Kriegsmann*, Z. anorg. allg. Chem. *299*, 78 (1959).

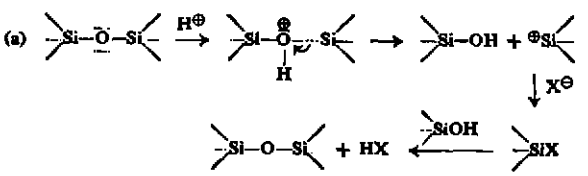
[21] *W. Meise*, unpublished.

Table 4. Si–O nuclear distances [Å] and Si–O–Si valence angles [°] in some siloxanes

Siloxane	Ref.	Valence angle Si–O–Si	Nuclear distance Si–O	Method
$[(CH_3)_2SiO]_3$	[23]	125 ± 5	1,66 ± 0.04	E[V]
$[(CH_3)_2SiO]_4$	[24]	142,5	1,65	R[K]
$[(CH_3)_2SiO]_n$	[25]	130 ± 10		R[K]
$(CH_3)_8Si_5O_6$	[26]	130 ± 4	1,64 ± 0.03	R[K]
$(CH_3)_3Si–O–Si(CH_3)_3$	[27]	130 ± 10	1,63 ± 0.03	E[V]
	[28]	131		D[F]
	[29]	137 ± 7		E[V]
$H_3Si–O–SiH_3$	[29]	142 ± 4	1,64 ± 0.01	E[V]
	[30]	144 ± 1	1,633 ± 0.001	E[V]
$Cl_3Si–O–SiCl_3$	[29]	175 ± 5	1,61 ± 0.03	R[K]
	[27]		1,64 ± 0.05	E[V]

E = Electron diffraction [V] = Vapor
R = X-ray diffraction [F] = Liquid
D = Measurement of dipole moment [K] = Crystal

toward protic acids. These cause cleavage when present in stoichiometric amounts. When, however, they are present in only catalytic amounts, they have (depending on the starting material and thermodynamic conditions) a polymerizing, depolymerizing, or equilibrating effect.



If an acid-activated Fuller's earth is allowed to act as catalyst on hot octamethylcyclotetrasiloxane, the ring is quickly split, and the compound polymerizes to long chain molecules, as indicated by a large viscosity increase. With a mixture of octamethylcyclotetrasiloxane and octaphenylcyclotetrasiloxane, only the former is attacked by the catalyst. The phenyl compound remains unaltered; this indicates that the siloxane bond is strengthened by the electronegative phenyl substituents. The fact that the phenyl-Si bond is split considerably more readily by acids than the methyl-Si bond is also in agreement with theory – an indication of the greater polarity of the former bond, in comparison with the latter.

Such relationships were thoroughly investigated with mixtures that contained octamethylcyclotetrasiloxane (hereafter designated as D_4 [31]), as well as the disiloxanes

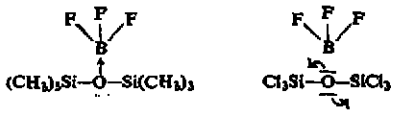
M–M	$(CH_3)_3Si–O–Si(CH_3)_3$
M'–M	$BrCH_2(CH_3)_2Si–O–Si(CH_3)_3$
M'–M'	$BrCH_2(CH_3)_2Si–O–Si(CH_3)_2CH_2Br$
M''–M''	$ClCH_2(CH_3)_2Si–O–Si(CH_3)_2CH_2Cl$

The mixtures were polymerized and equilibrated by the action of acid-activated Fuller's earth and/or sulfuric acid [33]. The more electronegative the substituent on the disiloxane and the greater the number of such substituents, the more the homopolymerization of the octamethylcyclotetrasiloxane speeds up in advance of the cleavage of the disiloxanes. The reactivity of the siloxanes toward protic acids decreases in the order

M–M > M–M' > M'–M' > M''–M'',

the contributions of the $d_\pi–p_\pi$ and covalent bond forms to the total Si–O–Si bond increase under the influence of electronegative substituents in just the same way.

Similarly, the reactivity of siloxanes towards Lewis acids depends on the nature of the substituents: hexamethyldisiloxane is readily split by boron trifluoride, while hexachlorodisiloxane does not react [34]. This means that in hexachlorodisiloxane, the electron-donor properties of the oxygen are no longer sufficient to effect an addition of BF_3:



An aminomethyl group acts on the Si–O–Si bond as a strong electron donor. That the Si–O–Si bond in an aminomethyldisiloxane is therefore highly polar can be inferred from the fact that it was not possible to obtain bis(aminomethyl)tetramethyldisiloxane from bis(chloromethyl)tetramethyldisiloxane and ammonia [35]. Only $NH_2CH_2(CH_3)_2Si–O–Si(CH_3)_3$ was obtained in this way [36]. Likewise, the synthesis of fourmembered rings which contain three dimethylsiloxane units and one (aminomethyl)methylsiloxane unit was successful [36]. These siloxanes tend to undergo molecular rearrangements to an unusual extent even at room temperature; in this case, also, the high polarity of the Si–O–Si bond in the neighborhood of an aminomethyl group is evident.

Influence of Cations in Silicate Lattices

The electronegativity of the metal atoms M that are present in silicates is almost always smaller than that of silicon (Table 5). Metal atoms therefore act as electron donors by comparison.

Table 5. Electronegativities

O	3.5	Ca	1.0
Fe(III)	1.9	Li	1.0
Si	1.8	Na	0.9
Fe(II)	1.8	K	0.8
Al	1.5	Cs	0.7
Mg	1.2		

[22] *H. Kriegsmann*, Z. Elektrochem., Ber. Bunsenges. physikal. Chem. *61*, 1088 (1957).

[23] *E. H. Aggarwal* and *S. H. Bauer*, J. chem. Physics *18*, 42 (1950).

[24] *H. Steinfink*, *B. Post*, and *J. Fankuchen*, Acta crystallogr. *8*, 420 (1955).

[25] *P. J. Flory*, *L. Mandelkern*, *J. B. Kinsinger*, and *B. W. Shultz*, J. Amer. chem. Soc. *74*, 3364 (1952).

[26] *W. L. Roth* and *D. Harker*, Acta crystallogr. *1*, 34 (1948).

[27] *K. Yamasaki*, *A. Kotera*, *M. Yokoi*, and *Y. Ueda*, J. chem. Physics *18*, 1414 (1950).

[28] *H. Freiser*, *M. V. Eagle*, and *J. Speier*, J. Amer. chem. Soc. *75*, 2824 (1953).

[29] *V. D. Frechette:* Non-Crystalline Solids. John Wiley, New York, London 1960, p. 74.

[30] *D. W. J. Cruickshank*, J. chem. Soc. (London) *1961*, 5486.

[31] D = bifunctional siloxane unit, *e.g.* $(CH_3)_2SiO$; M = monofunctional siloxane unit, for example, $(CH_3)_3SiO_{1/2}$; M' and M'' = M units substituted on the organic groups; see [32].

[32] *W. Noll:* Chemie und Technologie der Silicone. Verlag Chemie, Weinheim/Bergstr. 1960.

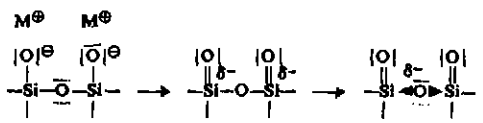
[33] *W. Simmler*, Makromolekulare Chem. *57*, 12 (1962).

[34] *H. Kriegsmann*, Z. anorg. allg. Chem. *299*, 149 (1959).

[35] *I. E. Noll*, *J. L. Speier*, and *B. F. Daubert*, J. Amer. chem. Soc. *73*, 3867 (1951).

[36] *P. D. George* and *J. R. Elliott*, J. Amer. chem. Soc. *77*, 3493 (1955).

A donor metal atom M polarizes the O–M bond; the electron "pressure" exerted by the donor atom acts on the Si–O(→M) bond in such a way that the contributions of the covalent and double-bond forms are increased (Scheme 2). In the Si–O(→Si) bond, the contribution of the polar form is increased. These effects should be the more evident the greater the difference in electronegativity between a silicon atom and an M atom present in a silicate.



Scheme 2. Influence of metal atoms (M) on the nature of the Si–O(→ M) and Si–O (→ Si) bonds.

It should be possible to prove the correctness of these ideas using infrared spectra. However, the data available up to the present are still insufficient (see, *e.g.* [37]). It was concluded from infrared spectroscopic investigations on alkali silicate glasses that the force constant of the Si–O(→M) bond – in agreement with theory – is greater than that of the Si–O(→Si) bond [38].

Differences in the type of bond should also cause perceptible differences in the internuclear distances, so that the Si–O(→M) distances in silicates with strong electron-donor atoms should be smaller than the Si–O(→Si) distances.

These questions can be cleared up only by a statistical study of selected data, since the differences that can be expected are small and fall within the range of the limits of error of the determinations of internuclear distances. In addition, silicates must be chosen for study which have polymeric anions that are free of, or at least poor in, aluminum atoms, because Al atoms replace Si isomorphically in the co-ordination tetrahedron and influence the distances. Some data, chiefly from recent structure investigations incorporating these provisions, have been compiled in Table 6.

Table 6. Si–O distances in silicate lattices [Å]

		Si–O(→ Si)	Average	Si–O(→ M)	Average
Tilleyite	$Ca_5[Si_2O_7/(CO_3)_2]$ [39]	1.65_5; $1.65_5 \pm 0.04$	1.65_5	1.58_0; 1.62_0 $1.59_5 \pm 0.02$	1.60_0
Sodium metasilicate	$Na_4[Si_2O_6]$ [40]	1.68; 1.67	1.67_5	1.57	1.57
Enstatite	$Mg_2[Si_2O_6]$ [41]	1.59; 1.59 1.63; 1.59	1.60	1.54; 1.54 1.53; 1.60	1.55
Klinoenstatite	$Mg_2[Si_2O_6]$ [42]	1.67; 1.63 ± 0.05	1.65	1.65; 1.61 ± 0.05	1.63
Diopside	$MgCa[Si_2O_6]$ [43] [42]	1.60; 1.64 1.60; 1.65 ± 0.05	1.62 1.62_5	1.57; 1.62 1.56; 1.59 ± 0.05	1.59_5 1.57_5
Pigeonite	$(Mg,Fe,Ca)_2[Si_2O_6]$ [42]	1.69; 1.59 ± 0.05	1.64	1.62; 1.55 ± 0.05	1.58_5
Cummingtonite	$(Fe,Mg)_7[Si_4O_{11}/OH]_2$ [44]	1.61_9; 1.64_2 1.61_9; 1.64_6 $1.63_8 \pm 0.02$	1.63_3	1.63_1; 1.62_7 $1.61_7 \pm 0.02$	1.62_5
Crocidolite	$(Na,K,Ca)_{3-4}$ Mg_6Fe^{2+} $(Fe^{3+}, Al)_{3-4}$ $[Si_{16}O_{44}/(OH)_4]$ [45]	1.65–1.66	1.65_5	1.59–1.60	1.59_5
Actinolite	$Na_2Ca_4(Mg,Fe)_{10}[Si_{16}O_{44}/(OH)_2/O_2]$ [46]	1.67	1.67	1.60	1.60
Lithium disilicate	$Li_2[Si_2O_5]$ [47]	1.67; 1.66; 1.69 1.57; 1.67; 1.66	1.65	1.56; 1.57	1.56_5
β-sodium disilicate	$Na_2[Si_2O_5]$ [48]	1.63; 1.62; 1.65 1.65; 1.64; 1.65	1.64	1.50; 1.52	1.51
Sanbornite	$Ba_4[Si_8O_{20}]$ [49]	1.68; 1.64; 1.65	1.66	1.60	1.60

The values in Table 6 do, in fact, show a difference in the average values of the distances for Si–O(→Si) and Si–O(→M), the former being greater than the latter. The differences are obviously related to the electronegativities of the metal atoms; they are especially large in lattices that contain strong electron donors, such as Li, Na, Ca, or Ba, and become smaller in lattices with weak electron donors, so that in the case of cummingtonite, for example, scarcely any difference can be observed. As an over-all average, the values are for

Si–O(→ Si): 1.64_4 Å,

and for

Si–O(→ M): 1.58_3 Å.

On the other hand, in modifications of SiO_2 (Table 2),

Si–O(→ Si) is 1.60_4 Å.

Inductive effects, which have only a very slight influence on the internuclear distances in silicate lattices, should be of more importance in lattices with polymeric groups of other elements (phosphates, arsenates, sulfates), in which bonds with greater double-bond character are present. The contributions of the double-bond form in the P–O and S–O bond are estimated, in comparison with those of the Si–O bond to be as follows [6]:

Si–O	32 %
P–O	44 %
S–O	54 %

[37] *B. D. Saksena*, Trans. Faraday Soc. *57*, 242 (1961).
[38] *J. Zarzycki* and *F. Naudin*, Verres et Réfractaires *1960*, 113.
[39] *J. V. Smith*, Acta crystallogr. *6*, 9 (1953).
[40] *A. Grund* and *M. M. Pizy*, Acta crystallogr. *5*, 837 (1952).
[41] *B. E. Warren* and *D. I. Modell*, Z. Kristallogr. *75*, 1 (1930).
[42] *N. Morimoto, D. E. Appleman*, and *H. T. Evans*, Z. Kristallogr. *114*, 138 (1960).
[43] *B. E. Warren* and *W. L. Bragg*, Z. Kristallogr. *69*, 168 (1928).
[44] *S. Ghose*, Acta crystallogr. *14*, 622 (1961).
[45] *E. J. W. Whittacker*, Acta crystallogr. *2*, 312 (1949).
[46] *J. Zussman*, Acta crystallogr. *8*, 301, (1955).
[47] *F. Liebau*, Acta crystallogr. *14*, 389 (1961).
[48] *A. Grund*, Bull. Soc. franç. Mineralog. Cristallogr. *77*, 775 (1954).
[49] *R. M. Douglass*, Amer. Mineralogist *43*, 517 (1958).

The differences in the distances of the P–O, As–O, and S–O bonds in the directions (→M) and (→P, As, S) are correspondingly large (Table 7).

Table 7. P–O, As–O, and S–O (X–O) distances in phosphate, arsenate, and sulfate lattices [Å]

	X–O(→X)	Average	X–O(→M)	Average
$RbPO_3$ [50]	1.62_1; 1.62_4	1.62_2	1.47_4; 1.43_8	1.45_6
$LiAsO_3$ [51]	1.73; 1.81	1.77	1.60; 1.60	1.60
$NaAsO_3$ [52]	1.76; 1.76	1.77	1.67; 1.67	1.67
	1.77; 1.79		1.67; 1.67	
$Na_4P_2O_7{\cdot}10\,H_2O$ [53]	1.63	1.63	1.47	1.47
$Na_5P_3O_{10}$ [54] I	1.62; 1.66	1.64	1.52; 1.45; 1.49	1.49
II	1.61; 1.68 ± 0.03	1.65	1.49; 1.49	1.49
			1.50 ± 0.03	
$(NH_4)_4P_4O_{12}$ [55]	1.63; 1.59	1.61	1.51; 1.44; 1.48	1.48
$K_2S_2O_7$ [56]	1.645 ± 0.005	1.645	1.438; 1.428	1.438
			1.447 ± 0.007	

From what has been said here, it appears doubtful whether it is correct to speak of a characteristic Si–O nuclear distance in silicates and silicic acids, for which an average value of 1.60 Å has so far been assumed [57]. At the very least, the value for the various modifications of SiO_2 should be considered separately from that for the silicates. It may likewise be incorrect to attempt to find one, and only one, characteristic Si–O nuclear distance for the whole range of the silicates. The length of this distance depends on the type of metal atoms bound in the lattice, and probably (something that requires further, more exact checking of the internuclear distances) on the number of metal atoms per silicon atom, or, in other words, on the degree of condensation of the siloxane groups.

It seems far less promising to discuss the influence of electron donors on the Si–O–Si valence angle in the silicate lattice than in the case of the siloxanes, since there the angle varies to a far greater extent [17]. The lower limit, it is true, is approximately 130°; however, larger angles are also observed [58]. These seem to be dependent on definite lattice types, rather than on the type of cation present. The largest angle measured so far, *viz.* 164°, occurs in a sorosilicate with Si_2O_7 anions.

There is a further problem of particular interest, namely, the extent to which the inductive influence of metal atoms on the relative contributions of the various bond types in the silicate lattice is also reflected in the chemical behavior of the compounds. Unfortunately, acid cleavage of silicates has been investigated quantitatively only with a few examples, as yet. The more qualitative data of the older literature on mineral chemistry furnish no adequate basis for discussion.

Weitz [59] carried out semiquantitative investigations of the action of weak acids (chiefly acetic acid) on silicate minerals with various anionic structures. By means of a molybdenic/tungstic-acid color test, it was determined whether and in what proportions orthomonosilicic acid, low molecular-weight oligosilicic acids, or high molecular-weight polysilicic acids were formed. The results therefore allowed conclusions to be drawn on the relative rate of decomposition of several silicate minerals (Table 8). The following fact seems noteworthy in connection with the theory developed here. Wollastonite and hypersthene are chain silicates which differ, apart from the periods of the $[SiO_3]_n^{2n-}$ chains, in the fact that wollastonite, with its calcium ions, contains stronger electron donors than the Mg–Fe^{2+}-silicate, hypersthene. Accordingly, in the lattice of the wollastonite, the Si–O–Si bonds should have a more strongly polar character, and therefore should be more readily split by acids than those in the lattice of the hypersthene. Actually, it was observed that, under similar conditions, only low molecular-weight and monomeric silicic acids appear in the acid extract of wollastonite, while the acid extract of hypersthene also contains polysilicic acid.

Table 8. Acid cleavage of several silicates [59]

Silicate	Cleavage gives		
	Monosilicic acid	Oligosilicic acid	Polysilicic acid
Olivine	·|·		
Garnet	|·		
Hemimorphite	·|·	·|·	
Wollastonite	(+)	·|·	
Hypersthene	+	·|·	+
Oligoclase	·|·	·|·	(+)
Leucite	+	|·	+

On passing from chain silicates to three-dimensional lattice structures, such as those of oligoclase and leucite, the increase of polarity of the anionic network by partial isomorphic replacement of Si by Al is superimposed on the influence of the metal atoms. This effect is apparently very strong, since, on treatment with acid, both oligoclase and leucite yield oligo- and monosilicic acids, in addition to polysilicic acids; they are therefore decomposed relatively quickly, without the distinct donor properties of K and Na being noticeable. Likewise, the old mineral chemical fact that decomposition of plagioclase with acid increases with increasing Al content and is greater than that of potash feldspar shows the strong influence exerted by substitution of Si by Al in the anionic group. A further example is the fact, which has also been known for a long time, that common augites, in which $[(Si,Al)_2O_6]$ chains are present, are considerably more readily cleaved by acids than enstatite $Mg_2[Si_2O_6]$. In this connection, investigations on the decomposition by acid of potash feldspars [60, 61] are especially impressive; from this research, it is evident that, contrary to earlier views, acids not only dissolve the potassium ions out of the lattice, but, in addition, decompose the $[(Si,Al)O_2]$ network relatively easily. It is also evident that extremely low molecular-weight silicic acids can be found in the acid extracts. Both the

[50] *D. E. C. Corbridge*, Acta crystallogr. *9*, 308 (1956).

[51] *W. Hilmer* and *K. Dornberger-Schiff*, Acta crystallogr. *9*, 87 (1956).

[52] *F. Liebau*, Acta crystallogr. *9*, 811 (1956).

[53] *D. M. MacArthur* and *C. A. Beevers*, Acta crystallogr. *10*, 428 (1957).

[54] *D. E. C. Corbridge*, Acta crystallogr. *13*, 263 (1960).

[55] *C. Romers*, *J. A. A. Ketelaar*, and *C. H. MacGillavry*, Acta crystallogr. *4*, 114 (1951).

[56] *H. Lynton* and *M. R. Truter*, J. chem. Soc. (London) *1960*, 5112.

[57] *J. V. Smith*, Acta crystallogr. *7*, 479 (1954).

[58] *F. Liebau*, Acta crystallogr. *14*, 1103 (1961).

[59] *E. Weitz*, *H. Franck*, and *M. Schuchard*, Chemiker-Ztg. *74* 256 (1950).

[60] *C. W. Correns*, Naturwissenschaften *28*, 369 (1940).

[61] *C. W. Correns* and *W. v. Engelhardt*, Chem. d. Erde *12*, 1 (1938).

ease of heterolytic cleavage of the silicate anion framework and the high degree of dispersion of the dissolved silicic acid are the results of a relatively strong polarity of the (Si,Al)–O–Si bond in the feldspar lattice.

Magmatic Crystallization Sequence from the Standpoint of Electronic Theory

From the thermodynamic point of view, the sequence of separation of the minerals from silicate melts is determined by the fact that those phases are invariably formed which have a minimum of free energy.

A discussion of the sequence of separation from the standpoint of the types and strengths of the bonds [62] starts from the fact that the Si–O(→Si) bond is the most stable in modifications of SiO_2, *i.e.* in lattices in which no inductive effect of foreign atoms occurs and with bonds to which a polar, a covalent, and a double-bond form make approximately equal contributions. The introduction of metal atoms reduces the stability of the structure. The stronger the electron donor action of the M atoms, and the greater the number of M atoms introduced per unit of Si, the lower the stability.

In the course of magmatic crystallization, there is an increase in the dimension number [*] of the anionic tetrahedral group in the separated crystalline phase, the sequence being neso → ino → phyllo → tectosilicates. This means that in nesosilicate with isolated SiO_4 tetrahedral anions, only Si–O(→M) bonds are present, and in SiO_2 only Si–O(→Si) bonds, and that, in between, the relative proportion of Si–O(→Si) bonds increases from the neso- to the tectosilicates. With increasing dimension number of the anion, the metal cations on the whole pass through a series

Mg, Fe → Na, Ca → K.

This is a transition from more strongly electronegative to more weakly electronegative types of atoms and denotes an increase in the electron-donor properties of the metal atoms.

This parallel between the dimension number of the anionic framework and the donor properties of the metal atoms can be explained in the following way. Depending on the Si/O ratio in the melt, small anions are formed in the first stages of crystallization. These contain no Si–O–Si bonds or only few of them. Metal atoms that are weak electron donors and accordingly increase the polarity of the Si–O–Si bond to only a slight extent are introduced preferentially into the separated crystal phase. As far as the principal elements present in naturally occurring magmas are concerned, these atoms are chiefly Mg and Fe.

As the dimension number of the anionic complex increases, the ability of the lattice to take up stronger electron donors also increases, since their inductive effect on the Si–O–Si bond becomes weaker the more strongly cross-linked the anion is and therefore the fewer M atoms per Si atom are present. Thus, Ca or, in part, Na can then be introduced into the inosilicates, in addition to Mg and Fe; these atoms, as well as K, become more and more prominent in the phyllosilicates. Finally, in the tectosilicates, the anionic groups are so strongly cross-linked that, even in the case of partial replacement of Si by Al, the ability to take up M atoms is very slight; hence, the compound is able to form a bond with even relatively strong electron donors, such as K or even Cs. The only cesium silicate known in nature, pollucite, is a tectosilicate.

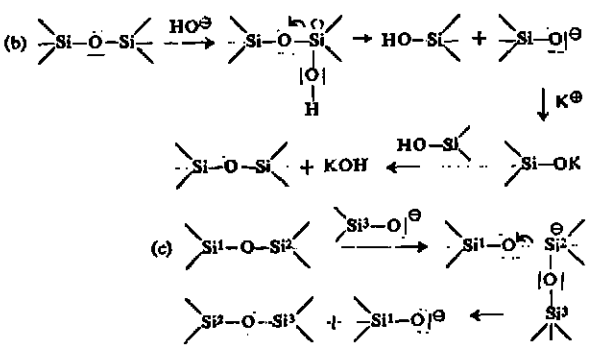
On crystallization of naturally occurring silicate magmas, therefore, the crystalline phases are formed in a sequence that is characterized by the smallest possible inductive weakening of the Si–O–Si bond by the metal atoms taken up.

Silicate Anions in Melts

According to a theory developed by *Bockris* et al. [63], discrete anion structures, consisting of separate rings or condensed ring systems, are present in silicate melts at certain Si/O ratios. This concept, however, contradicts the known fact that silicate crystals with anionic groupings of various dimension numbers can crystallize out from silicate melts at Si/O ratios between 1:3 and 1:2. Statistics on naturally occurring minerals show that silicate crystals with anions of larger size are considerably more common than those with anions of smaller size (*second selection principle*) [1].

This fact can be explained only by a theory that is not rigidly tied to the exclusive existence of definite anionic configurations in the melt. Such a theory can be developed and confirmed by the use of electronic theory and the known facts of methylpolysiloxane chemistry, if one regards liquid organopolysiloxanes (in a modification of *Goldschmidt*'s definition) as weakened models of silicate melts. Then these Si–O–Si bonds should also undergo cleavage and rearrangement under the influence of bases.

Such reactions, which give products corresponding to those of the acid-catalyzed rearrangement [Eq. (a)], are initiated by nucleophilic addition of basic oxygen on to a Si atom, and when using methylpolysiloxanes and KOH, proceed according to [Eq. (b)], or, with potassium dimethylsiliconate as catalyst, according to Eq. (c).



[62] See also *H. Ramberg*, J. Geology *60*, 331 (1952).

[*] The dimension number denotes how many dimensions of the molecule are infinite. Zero-dimensional: neso-, soro-, and cyclosilicates; one-dimensional: inosilicates; two-dimensional: phyllosilicates; three-dimensional: tectosilicates; cf. [1].

[63] *J. O'M. Bockris:* Modern Aspects of Electrochemistry. Butterworths, London 1959, p. 243 *et seq.*

Accordingly, if the Si–O(→M) bonds of the silicate melts contain a sufficient number of "basic" oxygen or M atoms which are electron donors with respect to Si, then rearrangement reactions occur by regular breaking and reforming of Si–O–Si bonds. At a given Si/O ratio, this leads to the occurrence of *partition equilibria between anionic groups of different structures*, in which the proportion of each structural type is dependent on the kind of cations contained in the melt, on the temperature, and on the pressure. On cooling of the melt and separation of a crystalline phase, that anion type is removed which yields a crystalline phase that is stable under the given conditions, while at the same time a new partition equilibrium is constantly set up in the melt.

Equilibria between cyclic and chain structures are possible especially in metasilicate melts with the ratio Si:O = 1:3. If phases with chain structures are formed predominantly on crystallization of these melts (second selection principle), this can also be considered analogous to the known facts on the equilibrium in liquid methylpolysiloxanes, where the tendency of Si–O–Si bonds of the greatest possible size to be synthetized predominates at low temperatures.

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Metal π-Complexes with Di- and Oligo-olefinic Ligands [*]

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To the somewhat casual observer, the concept "metal π-complex" is primarily associated with the names "ferrocene" and "dibenzenechromium". The preparation of these two compounds was in fact the starting point of a development which has had fruitful effects on theoretical as well as preparative chemistry and the limits of which are not yet in sight. In recent years, many straight-chain and cyclic olefins with varying numbers of double bonds have been added to the list of ligands in metal π-complexes, besides such "aromatic" systems as the cyclopentadienyl anion, benzene, and the tropylium cation. The literature in this area is already so copious that it seems advisable to adopt a division into compounds with mono-olefins and those with di- and oligo-olefins. The present review is concerned exclusively with the latter group.

Historical

Olefin-metal compounds originated in the year 1827. The Danish chemist *Zeise* reported [1] that, after boiling an ethanolic solution of chloroplatinic acid and adding KCl, he had been able to isolate a crystalline substance with the formula $KCl \cdot PtCl_2 \cdot C_2H_4 \cdot H_2O$ (generally known today as "*Zeise*'s salt"). There were at first some doubts as to the composition of this new substance and *Liebig*, for example, believed that "...*Zeise*'s formula is obviously based only on a conjecture" [2]. Despite all objections, *Zeise*'s analytical results remained the "truth", and not a "fog", as *Liebig* supposed. *Birnbaum* was able to prepare the analogous propyleneplatinum and amyleneplatinum compounds in 1868 [3].

However, it was not until 1908 that the first diolefin-metal complex was described. *Hofmann* and *von Narbutt* [4] had treated "potassium platinum chloride" with dicyclopentadiene in various alcohols, and with propanol had obtained a crystalline substance of composition $C_{10}H_{12}PtCl_2$. By analogy with the behavior of mercury salts toward olefins, they assumed the addition of a chlorine atom and a PtCl residue onto a double bond. It was only in 1956 that the structure of $C_{10}H_{12}PtCl_2$ was recognized by *Doyle* and *Jonassen* [5] to be a diolefin-metal halide complex. This was later confirmed by the investigations of its crystalline structure by *Baenziger* [6].

The difficulties, which, even at the beginning of the twentieth century, were still associated with a satisfactory explanation of the bonding of unsaturated organic molecules to a metal atom, are probably responsible for the fact that it was not until 1930 that a diolefin -metal complex was again mentioned in the literature. *Reihlen* and co-workers [7] at-

[*] A monograph by *E. O. Fischer* and *H. Werner* on this same subject will be published shortly by Verlag Chemie, Weinheim/Bergstr.

[1] *W. C. Zeise*, Pogg. Annalen *9*, 632 (1827).

[2] *J. Liebig*, Liebigs Ann. Chem. *23*, 12 (1837).

[3] *K. Birnbaum*, Liebigs Ann. Chem. *145*, 67 (1868).

[4] *K. A. Hofmann* and *J. v. Narbutt*, Ber. dtsch. chem. Ges. *41*, 1625 (1908).

[5] *J. R. Doyle* and *H. B. Jonassen*, J. Amer. chem. Soc. *78*, 3965 (1956).

[6] *N. C. Baenziger, J. R. Doyle, G. F. Richards*, and *C. L. Carpenter:* Advances in the Chemistry of the Coordination Compounds. The Macmillan Company, New York 1961, p. 136.

[7] *H. Reihlen, A. Gruhl, G. v. Hessling*, and *O. Pfrengle*, Liebigs Ann. Chem. *482*, 161 (1930).

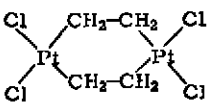
tempted to settle the question whether the carbonyl groups in $Fe(CO)_5$ are bonded to the metal through the carbon or the oxygen. Among other experiments, they treated $Fe(CO)_5$ with butadiene in a sealed tube and obtained a butadiene iron tricarbonyl as a yellow liquid that was stable to air. They assumed a ring closure of the butadiene through the iron, involving Fe–C σ-bonds.

Butadiene was also the object of numerous investigations into the chemistry of complexes during the years which followed. *Gelman* and co-workers [8] treated $(NH_4)_2[PtCl_4]$ with C_4H_6 and obtained, together with small quantities of $[C_4H_6PtCl_2]_2$, a very stable substance with the composition $(NH_4)_2[C_4H_6Pt_2Cl_6]$, in which a butadiene bridge was assumed to exist between the two metal atoms. Subsequently, they prepared numerous mono-olefin, several 1,5-hexadiene compounds and at least twelve C_4H_6-Pt complexes, and discussed the bonding of the olefinic ligands to the central atom [8–15].

After 1945, it was primarily *Chatt* and his co-workers in England who contributed to the theoretical and experimental expansion of the field. They investigated, among other things, the tendency of non-conjugated diolefins to form complexes, and showed that, for example, 1,5-cyclo-octadiene is highly suited as a ligand for transition metal-halogen compounds, because of the favorable steric arrangement of its double bonds [16–19]. Nevertheless, their attempts to prepare 1,5-cyclo-octadiene-metal carbonyls remained without success [19]. However, in 1958, *Hallam* and *Pauson* succeeded in isolating a tricarbonyl iron complex analogous to $C_4H_6Fe(CO)_3$ and containing a cyclic conjugated diolefin, 1,3-cyclohexadiene [20]. In 1958, soon after the preparation of $C_6H_6Cr(CO)_3$ [21], using an analogous reaction, *Wilkinson* obtained, a red, diamagnetic material, $C_7H_8Mo(CO)_3$, the first cycloheptatriene-metal complex [22]. Reports appeared in the following year concerning metal carbonyl compounds containing cyclo-octatetraene [23–25] and cyclo-octatriene [26–28] as ligands. Attempts to coordinate smaller polyunsaturated rings with a transition metal atom led to the preparation in 1959 of π-complexes of cyclopentadiene [29–31] and of cyclobutadiene [32–35]. This achievement also simultaneously solved a "classical" problem of organic chemistry, namely the question as to the existence of cyclobutadiene and its derivatives. Recently, larger rings, such as 1,5,9-cyclododecatriene, heterocyclic diene compounds, and straight chain di- and oligo-olefins have also been used as ligands in π-complexes.

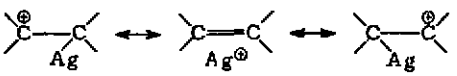
The Nature of the Olefin-Metal Bond

Until very recently, there was a tendency to consider olefin-metal compounds as "organic molecular compounds" rather than as complexes, since an olefinic residue, unlike other ligands, does not have a free electron pair. Moreover, various bonds and structures suggested expressed a postulated relationship to the real organometallic compounds, which was suspected since the work of *Zeise*. As late as 1936, *Kharasch* [36] proposed structure *(1)* for bis(ethylene)platinum dichloride, with ethylene bridges and Pt–C σ-bonds.



(1)

It was only by application of quantum mechanical methods that a better approach towards solution of the bonding was found. An initial attempt was made by *Winstein* and *Lucas* [37], who explained the existence of olefin-silver complexes *(2)* on the basis of resonance stabilization.



(2)

Pitzer [38] explained the stability of the olefin-metal bond by applying the concept of the "protonated double bond", and spoke of an "argentated double bond". The free s-orbital of the silver, analogous to the free s-orbital of the proton, was asserted to make it possible for a bond to be formed with the olefin.

[8] *A. D. Gelman*, Dokl. Akad. Nauk S.S.S.R. *23*, 532 (1939); Chem. Zbl. *1940*, I, 1809.

[9] *A. D. Gelman*, Ann. Secteur Platine autres Métaux précieux *17*, 5 (1940).

[10] *A. D. Gelman*, Dokl. Akad. Nauk S.S.S.R. *31*, 760 (1941); Chem. Zbl. *1943*, I, 1362.

[11] *A. D. Gelman*, Dokl. Akad. Nauk S.S.S.R. *33*, 462 (1941).

[12] *A. D. Gelman*, Dokl. Akad. Nauk S.S.S.R. *38*, 272 (1943).

[13] *A. D. Gelman*, Dokl. Akad. Nauk S.S.S.R. *38*, 243 (1943).

[14] *A. D. Gelman* and *E. A. Mejlach*, Ann. Secteur Platine autres Métaux précieux *20*, 21 (1947).

[15] *A. D. Gelman*, Ann. Secteur Platine autres Métaux précieux *20*, 139 (1947).

[16] *J. Chatt* and *L. M. Venanzi*, Nature (London) *177*, 852 (1956).

[17] *J. Chatt*, *L. M. Vallarino*, and *L. M. Venanzi*, J. chem. Soc. (London) *1957*, 2496.

[18] *J. Chatt*, *L. M. Vallarino*, and *L. M. Venanzi*, J. chem. Soc. (London) *1957*, 3413.

[19] *J. Chatt* and *L. M. Venanzi*, J. chem. Soc. (London) *1957*, 4735.

[20] *B. F. Hallam* and *P. L. Pauson*, J. chem. Soc. (London) *1958*, 642.

[21] *E. O. Fischer* and *K. Öfele*, Chem. Ber. *90*, 2532 (1957).

[22] *E. W. Abel*, *M. A. Bennet*, and *G. Wilkinson*, Proc. chem. Soc. (London) *1958*. 152.

[23] *T. A. Manuel* and *F. G. A. Stone*, Proc. chem. Soc. (London) *1959*, 90.

[24] *M. D. Rausch* and *G. N. Schrauzer*, Chem. and Ind. *1959*, 957.

[25] *A. Nakamura* and *N. Hagihara*, Bull. chem. Soc. Japan *32*, 881 (1959).

[26] *E. O. Fischer* and *C. Palm*, Z. Naturforsch. *14b*, 347 (1959).

[27] *E. O. Fischer* and *C. Palm*, Z. Naturforsch. *14b*, 598 (1959).

[28] *E. O. Fischer*, *C. Palm*, and *H. P. Fritz*, Chem. *92*, 2645 (1959).

[29] *E. O. Fischer*, *U. Zahn*, and *F. Baumgärtner*, Z. Naturforsch. *14b*, 133 (1959).

[30] *E. O. Fischer* and *U. Zahn*, Chem. Ber. *92*, 1624 (1959).

[31] *M. L. H. Green*, *L. Pratt*, and *G. Wilkinson*, J. chem. Soc. (London) *1959*, 3753.

[32] *R. Criegee* and *G. Schröder*, Angew. Chem. *71*, 70 (1959).

[33] *R. Criegee* and *G. Schröder*, Liebigs Ann. Chem. *623*, 1 (1959).

[34] *M. Avram*, *E. Marica*, and *C. D. Nenitzescu*, Chem. Ber *92*, 1088 (1959).

[35] *W. Hübel* et al., J. inorg. nuclear Chem. *9*, 204 (1959.

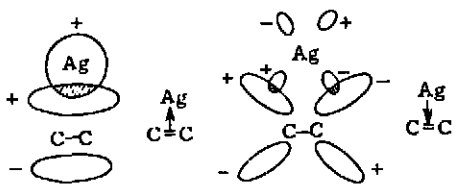
[36] *M. S. Kharasch* and *T. A. Ashford*, J. Amer. chem. Soc. *58*, 1735 (1936).

[37] *S. Winstein* and *H. J. Lucas*, J. Amer. chem. Soc. *60*, 836 (1938).

[38] *K. S. Pitzer*, J. Amer. chem. Soc. *67*, 1127 (1945).

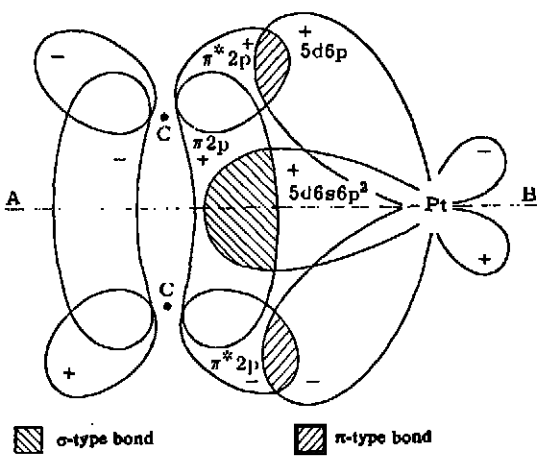
That π-electrons can act as donors towards an acceptor atom was clearly stated for the first time by *Dewar* [39] and *Walsh* [40]. According to *Walsh*, the coordinated bond of an olefin to a metal can be compared to that of a complex ligand such as ammonia, since the π-electrons, *e.g.* in ethylene, occupy an orbital with an ionization potential of 10.45 v, which corresponds to that of the free electron pair in the NH_3 molecule (10.8 v).

However, even these attempts to explain the bonding of unsaturated ligands to a metal atom remained unsatisfactory. A better picture, based on molecular orbital theory, was developed by *Dewar* in 1951 [41]. He divided the olefin-metal bond into a σ-portion and a π-portion. The former was said to arise by overlapping of π-electrons of the olefin with free orbitals of the central atom, and the latter by combination of occupied d-states of the metal with antibonding orbitals of the olefin *(3)*.



(3)

Chatt and *Duncanson* [42] extended this concept to olefin-platinum complexes *(4)*. The normal σ-type bond is formed here with a free [5d6s6p²] hybridized orbital of the platinum, while the π-bond results from combination of an occupied [5d6p] electron level of the platinum with an antibonding orbital of the olefin. It is seen in *(4)* that this antibonding π-orbital, which is not occupied by electrons in the free molecule, has d-type symmetry, which appears favorable for an overlapping with a pure d- or a dp-hybrid orbital [43].



(4)

The ideas presented in Figure 4 were mainly supported by infrared spectroscopic investigations. Thus, the C=C valence vibration of many olefin-platinum complexes occurs at wave numbers which are lower by about 145 cm^{-1} than those in the free olefins. The weakening of the double bond indicated by this is about twice the magnitude of that occurring in analogous olefin silver complexes. This is evidence for a stronger bonding of the unsaturated ligand to Pt than to Ag. The weakening of the double bond resulting from lowering of the electron density in the bonding molecular π-orbitals was also confirmed by X-ray investigation. Thus, the C=C distance of 1.34 Å in free ethylene is increased to 1.47 Å in $[C_2H_4PtCl_2NH(CH_3)_2]$ [44].

The concepts explained above are also valid for di- and oligo-olefin complexes. Their greater stability (in comparison with mono-olefin compounds) is reflected, for example, in the molecular spectra by a further lowering of wave number for the C=C valence vibration [45].

$K[C_2H_4PtCl_3]$	1511 cm^{-1}	C_2H_4	1623 cm^{-1}
$K_2[C_4H_6(PtCl_3)_2]$	1473 cm^{-1}	C_4H_6	1597 cm^{-1}
$C_5H_5MnC_2H_4(CO)_2$	1510 cm^{-1}		
$C_5H_5MnC_4H_6(CO)$	1466 cm^{-1}		

It is essential to distinguish between conjugated and nonconjugated ligands in di- and oligo-olefin-metal complexes. In nonconjugated ligands, interchange of π-electrons with each other is prohibited (with a few restrictions), and the bonding problem is similar to that of two isolated double bonds, whereas their mutual influence must be considered when conjugation is present. Extensive delocalization of the π-electron system in such instances was proposed for the first time by *Hallam* and *Pauson* [20] in the case of $C_4H_6Fe(CO)_3$. Since they obtained analogous compounds of comparable stability only with conjugated diolefins and not with others, these authors assumed bonding between the butadiene and the iron similar to that found in arene complexes, *i.e.* with overlapping of all of the π-electrons with unoccupied orbitals of the metal. *Mills* and *Robinson* confirmed this interpretation by an X-ray structural analysis [46]. According to the latter, the iron atom in $C_4H_6Fe(CO)_3$ is equidistant from all four carbon atoms of the butadiene and all the C–C distances are of equal length, facts which can only be explained by complete delocalization of the π-electrons. A similar type of bonding is also to be assumed in other oligo-olefin-metal compounds, *e.g.* those of cyclo-octatetraene, cyclopentadienone, and tropone. Although analogies to the true arene complexes are present, caution is recommended with the concept of the "quasi-aromatic character" of olefinic systems. Thus, investigation of the crystal structure of $C_7H_8Mo(CO)_3$ has shown [47] that cycloheptatriene bound in a complex is actually more of a triene than an aromatic system.

The *Dewar-Chatt* bond representations for di- and oligo-olefin-metal compounds are supported by other results and considerations. As seen in *(4)*, the degree of overlapping between the π-electrons of the ligand and unoccupied states of the metal is considerably greater than in orbitals shared through back donation. The

[39] *M. J. S. Dewar*, J. chem. Soc. (London) *1946*, 406.

[40] *A. D. Walsh*, Nature (London) *159*, 165, 712 (1947).

[41] *M. J. S. Dewar*, Bull. Soc. chim France *18*, C 79 (1951).

[42] *J. Chatt* and *L. A. Duncanson*, J. chem. Soc. (London) *1953*, 2939.

[43] See *L. E. Sutton:* Chemische Bindung und Molekülstruktur. Springer-Verlag, Berlin 1961

[44] *P. R. H. Alderman, P. G. Owston*, and *J. M. Rowe*, Acta crystallogr. (Copenhagen) *13*, 149 (1960).

[45] *M. Herberhold*, Diploma Thesis, Universität München, 1961.

[46] *O. S. Mills* and *G. Robinson*, Proc. chem. Soc. (London) *1960*, 421.

[47] *J. D. Dunitz* and *P. Pauling*, Helv. chim. Acta *43*, 2188 (1960).

stronger donor effect of the olefin in comparison with the metal denotes a transfer of the partial negative charge to the central atom resulting in a more positive nature of the unsaturated residue. The transition metals, which are only weakly electronegative, attempt to distribute the negative charge among the ligands. This signifies a strengthening of the back donation in the direction of the olefinic groups, and thereby an increase in double bond character.

As other ligands, halogens and carbon monoxide are of principal importance. Because of their electronegative character, both are suitable for taking over charge transfered from the central atom and can thus stabilize the olefin-metal bond. The numerous known complex compounds of the type [(diene)MeX_2] are distinguished, for example, by significant dipole moments, the olefin forming the positive and the halogen the negative portion of the dipole. Replacement of the halogen with more electropositive residues lowers the stability, as shown, for example, by comparing the very stable cyclo-octadienepalladium dichloride $C_8H_{12}PdCl_2$ [18] and the unstable cyclo-octadiene dimethylpalladium $C_8H_{12}Pd(CH_3)_2$ [48].

With di- and oligo-olefin-metal carbonyls the charge displacement olefin → metal → CO is confirmed not only by dipole measurements but also by infrared spectroscopic investigations and X-ray structural analyses. According to *R. D. Fischer* [49], the frequencies of the completely symmetrical CO vibration in these compounds are about 40 to 60 wave numbers smaller than those in pure carbonyls; this corresponds to a decrease in the CO force constant and thus in the degree of bonding of the CO. Obviously, the greater the donor character of a complex-bound olefin, the more the unhybridized d-electrons of the metal can contribute towards the formation of a metal-CO partial double bond. This is accompanied by a corresponding diminution of the degree of bonding of the CO, and, in keeping with the tetravalency of carbon, a corresponding displacement in the direction of the resonance structure *(5b)* [50]:

(5a) *(5b)*

Stabilization of the olefin-metal bond must therefore coincide with a strengthening of the metal-CO bond. Thus, it is understandable that with metal carbonyls, any increase in substitution has the result that the remaining CO groups become more strongly bound since they must take over more of the negative charge from the central atom. Up to now, it has been possible to effect complete replacement of the CO residues by olefinic ligands only in bis(duroquinone)nickel(0), which is obtainable from $Ni(CO)_4$ and duroquinone [51], and a few analogous compounds. Replacement of the carbon monoxide with cyclopentadiene, for example, always leads to the formation of aromatic, and not olefinic, complexes.

Dipole measurements in the author's laboratory confirm the "electronegative" character of the CO groups, already deduced from infrared spectroscopic investigations. The moments of numerous di- and oligo-olefin-metal carbonyls are sometimes quite considerable and can be explained only on the assumption that the CO ligands can accept a large amount of the increase in negative charge resulting from complex formation. In all the complexes investigated, any lowering of the CO frequency is also associated with an increase in dipole moment.

The strengthening of the bond between the metal and the carbon of the CO group is also evident from the structural analysis of cycloheptatrienemolybdenum tricarbonyl [47]. Mo-C bond lengths of 1.986, 1.986, and 1.950 (± 0.02) Å were found; in comparison, the length of the Mo-C bond in $Mo(CO)_6$ is 2.08 ± 0.04 Å [52].

The fact that replacement of a CO group in di- and oligo-olefin-metal carbonyls with a triphenylphosphine residue is associated with considerable stabilization of the complex is a further confirmation of the bonding theory of *Dewar* and *Chatt*. Because of its vacant 3d-orbital, phosphorus is much more capable of forming double bonds than carbon and can more easily accept the negative charge of the central atom caused by the donor effect of the olefin. Thus, for example, cyclopentadieneiron tricarbonyl-$C_5H_6Fe(CO)_3$ is an unstable liquid [53]; cyclopentadiene(triphenylphosphine)iron dicarbonyl $C_5H_6Fe(CO)_2P(C_6H_5)_3$, on the other hand, is a stable, crystalline substance [54]. Again, a compound $C_8H_{12}Ni[P(C_6H_5)_3]_2$ is known [55], while $C_8H_{12}Ni(CO)_2$ has not yet been prepared.

An olefin-metal bond can also be partly strengthened by aromatic residues, outstanding examples being the numerous representatives of the type $C_5H_5Co(olen)$, where olen = C_4R_4, C_5H_6, C_5R_4O, C_6H_8, nor-C_7H_8, C_8H_8, C_8H_{10}, C_8H_{12}, or $C_4R_2H_4$. Among similar compounds, each with a six-membered aromatic ring, only $C_6H_6RuC_6H_8$ [56] and $C_6H_6FeC_6H_8$ [56a] are known so far. Back donation of d-electrons of the central atom to unoccupied states of the aromatic ligand appears to be possible here to only a small degree.

The question of the spatial orientation of complex-bound unsaturated ligands was linked with the bonding problem. An answer to this question was found on the basis of *Hückel*'s theory of the double bond, according

[48] *G. E. Coates:* Organometallic Compounds. 2nd Ed., Methuen London, 1960, p. 320.

[49] *R. D. Fischer*, Ph.D. Thesis, Universität München, 1961.

[50] See *R. D. Fischer*, Chem. Ber. *93*, 165 (1960).

[51] *G. N. Schrauzer* and *H. Thyret*, J. Amer. chem. Soc. *82*, 6420 (1960).

[52] *L. O. Brockway*, *R. V. G. Ewens*, and *M. Lister*, Trans. Faraday Soc. *34*, 1350 (1938).

[53] *A. H. Filbey*, *J. C. Wollensak*, and *K. A. Keblys:* Abstracts of Papers, 138th Meeting of the American Chemical Society, New York, September 1960, p. 54-P.

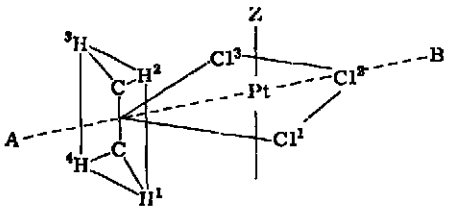
[54] *A. Davison*, *M. L. H. Green*, and *G. Wilkinson*, J. chem. Soc. (London) *1961*, 3172.

[55] *G. Wilke*, *E. W. Müller*, and *M. Kröner*, Angew. Chem. *73*, 33 (1961).

[56] *D. Jones* and *G. Wilkinson*, Chem. and Ind. *1961*, 1408.

[56a] *E. O. Fischer* and *J. Müller*, Z. Naturforsch. *17b*, 776 (1962).

to which the π-electron density is greatest in the plane perpendicular to that of the C=C bond. Thus, for example, in a planar, dsp^2 hybridized mono-olefin complex, the double bond must be perpendicular to the plane formed by the metal and the remaining ligands, since the most favorable conditions for overlapping are attained in this way. On this basis, *Chatt* [42] proposed a molecular configuration for the ethyleneplatinum trichloride anion, which is depicted in *(6)*. The plane of the H and C atoms lies parallel to the plane Cl^1ZCl^3, and the line of the carbon atoms is presumed to be closer to the Pt.



(6)

Similar concepts apply to compounds of the type [olenMeX$_2$]. Analysis of the crystal structure of norbornadienepalladium dichloride (nor-$C_7H_8PdCl_2$) has shown [57] that here, too, both double bonds lie perpendicular to the plane formed by the Pd and Cl atoms. A square arrangement with a dsp^2 hybridized central atom is generally favored in di- and oligo-olefin-metal halide complexes.

The tendency towards completing shells is decisive in the formation of di- and oligo-olefin-metal carbonyls. For this reason, anomalous coordination numbers are not rare in such compounds, as is also the case with pure carbonyls and arene-metal carbonyls; for example, 5 for di- or oligo-olefin-iron tricarbonyls or 7 for diolefin-cyclopentadienylvanadium dicarbonyls, where the C_5H_5 residue is considered to be trivalent. All complexes of this kind are diamagnetic.

Preparative Methods [*]

1. (olen)$_m$MeX$_n$

In this type of compound, the central atoms are always elements of the 7th, 8th, and 1st subgroups. In most cases, they have their normal valences. However, through favorable steric arrangements, anomalous oxidation numbers can also be stabilized; *e.g.* Rh(I) in [nor-$C_7H_8RhCl]_2$[58],[$C_8H_{12}RhCl]_2$[16,19],[$C_8H_8RhCl]_2$ [58], [$C_{10}H_{12}RhCl]_2$ [19]; Ru(II) in [nor-$C_7H_8RuCl_2]_n$ [58], [$C_8H_{12}RuCl_2]_n$ [59], [$C_8H_8RuCl_2]_n$ [59]; and Re(II) in [$(C_{10}H_{12})_2ReCl_2$] [60]. In general, the coordination numbers 2, 4 (square planar), and 6 (octahedral) predominate.

a) *Reaction of a Metal Salt or a Complex Salt with a Di- or Oligo-olefin*

α) Without Solvent

Anhydrous copper halides react with gaseous and liquid butadiene [61,62], with norbornadiene (nor-C_7H_8) [63], 1,5-cyclo-octadiene [63], cyclo-octatetraene [63], or dicyclopentadiene [63].

$$m\ CuX + olen \rightarrow olen(CuX_m)$$

(olen = C_4H_6, nor-C_7H_8, 1,5-C_8H_{12}, C_8H_8, or $C_{10}H_{12}$; X = Cl or Br; m = 1 or 2)

Furthermore $C_{10}H_{12}\cdot AgNO_3$ [37] or $C_{10}H_{12}\cdot AgClO_4$ [37] can be obtained by direct reaction of $AgNO_3$ or $AgClO_4$, respectively, with dicyclopentadiene, and $(C_{10}H_{12})_2ReCl_2$ [60] from $ReCl_3$ and dicyclopentadiene.

β) In Water

Water has served most often as solvent in the preparation of silver nitrate adducts with di- and oligo-olefins.

$$m\ AgNO_3 + n\ olen \xrightarrow{H_2O} (olen)_n(AgNO_3)_m$$

(olen = nor-C_7H_8 [58,64], 1,3-C_8H_{12} [65], 1,4-C_8H_{12} [65], 1,5-C_8H_{12} [66,67], C_8H_8 [68,69], C_8H_7R [70–72]; m = 1, 2 or 3; n = 1 or 2).

The preparation of $C_8H_8PtCl_2$ [73] or $C_6H_{10}PtCl_2$ [74] from $K_2[PtCl_4]$ and cyclo-octatetraene or 1,5-hexadiene, respectively, has also been carried out in water,

$$K_2[PtCl_4] + olen \xrightarrow{H_2O} [olenPtCl_2] + 2\ KCl$$

(olen = C_8H_8 or C_6H_{10})

as has that of $C_8H_{12}PdCl_2$ [18] from $(NH_4)_2[PdCl_4]$ and 1,5-cyclo-octadiene. A hydrated olefin complex, C_4H_6.

---

[57] *N. C. Baenziger, J. R. Doyle,* and *C. Carpenter,* Acta crystallogr. (Copenhagen) *14,* 303 (1961).

[*] The following abbreviations are used: olen = oligo-olefin; dien = diolefin; *p*-tol = *p*-toluidine; Me = transition metal; X = univalent negatively charged residue; L = univalent neutral ligand; m, n, x = whole numbers.

[58] *E. W. Abel, M. A. Bennet,* and *G. Wilkinson,* J. chem. Soc. (London) *1959,* 3178.

[59] *M. A. Bennet* and *G. Wilkinson,* Chem. and Ind. *1959,* 1516.

[60] *R. Colton, R. Levitus,* and *G. Wilkinson,* Nature (London) *186,* 233 (1960).

[61] *E. R. Gilliland, H. L. Bliss,* and *C. E. Kip,* J. Amer. chem. Soc. *63,* 2088 (1941).

[62] *P. E. Slade jr.* and *H. B. Jonassen,* J. Amer. chem. Soc. *79,* 1277 (1957).

[63] *G. N. Schrauzer* and *S. Eichler,* Chem. Ber. *95,* 260 (1962).

[64] *J. G. Traynham* and *J. R. Olechowski,* J. Amer. chem. Soc. *81,* 571 (1959).

[65] *W. O. Jones,* J. chem. Soc. (London) *1954,* 312.

[66] *A. C. Cope* and *L. L. Estes Jr.,* J. Amer. chem. Soc. *72,* 1128 (1950).

[67] *A. C. Cope, C. L. Stevens,* and *F. A. Hochstein,* J. Amer. chem. Soc. *72,* 2510 (1950).

[68] *W. Reppe, O. Schlichting, K. Klager,* and *T. Toepel,* Liebigs Ann. Chem. *560,* 1 (1948).

[69] *A. C. Cope* and *F. A. Hochstein,* J. Amer. chem. Soc. *72,* 2515 (1950).

[70] *A. C. Cope* and *M. R. Kinter,* J. Amer. chem. Soc. *73,* 3424 (1951).

[71] *A. C. Cope* and *H. C. Campbell,* J. Amer. chem. Soc. *74,* 179 (1952).

[72] *A. C. Cope* and *D. J. Marshall,* J. Amer. chem. Soc. *75,* 3208 (1953).

[73] *K. A. Jensen,* Acta chem. scand. *7,* 868 (1953).

[74] *K. A. Jensen,* Acta chem. scand. *7,* 866 (1953).

2 $CuCl \cdot 4 H_2O$, has been isolated [75] by the action of butadiene on an aqueous copper chloride solution.

γ) In an Organic Medium

Alcohols, acetone, and acetic acid have been employed successfully as solvents for the preparation of di- and oligo-olefin-metal halides. $Na_2[PdCl_4]$ reacts, for example, with norbornadiene in methanol [76], as well as with 1,5-cyclo-octadiene or dicyclopentadiene in acetone [18].

$$Na_2[PdCl_4] + dien \rightarrow [dienPdCl_2] + 2\,NaCl$$
(dien = nor-C_7H_8, 1,5-C_8H_{12} or $C_{10}H_{12}$).

The analogous Pt complexes are likewise accessible in propanol or isopropanol, while α-$C_{10}H_{16}PtCl_2$ [77] and

$$Me_2[PtCl_4] + dien \rightarrow [dienPtCl_2] + 2\,MeCl$$
(Me = Na or K; dien = 1,5-C_6H_{10} [17], 1,5-C_8H_{12} [17], or $C_{10}H_{12}$ [4, 17])

nor-$C_7H_8PtCl_2$ [58] are obtained from $PtCl_4$ and dipentene or norbornadiene, respectively, in glacial acetic acid. Dimeric compounds $[olenRhCl]_2$ are formed in ethanol from $RhCl_3$ and norbornadiene [58], 1,5-cyclo-octadiene [16, 19], cyclo-octatetraene [58], or dicyclopentadiene [19]. The complexes $[nor\text{-}C_7H_8RuX_2]_n$ and $[C_8H_{12}RuX_2]_n$ (X = Cl, Br, or I) are formed from ruthenium trihalides and norbornadiene [58] and 1,5-cyclo-octadiene [59], respectively. The adducts $C_5H_6 \cdot AgBF_4$ [78], $C_5H_6 \cdot AgClO_4$ [79], and $C_6H_8 \cdot AgBF_4$ [78], which are sensitive to hydrolysis, were obtained in proton-inactive solvents such as diethyl ether or benzene.

b) *Displacement Reactions*

In 1938, *Kharasch* [80] described a generally applicable method for the preparation of mono-olefin palladium complexes from $[(C_6H_5CN)_2PdCl_2]$. Later, replacement of the benzonitrile residues was also achieved with di- and oligo-olefins.

$$[(C_6H_5CN)_2PdCl_2] + olen \rightarrow [olenPdCl_2] + 2\,C_6H_5CN$$
(olen = C_4H_6 [62], 1,5-C_6H_{10} [74], nor-C_7H_8 [58, 76], 1,5-C_8H_{12} [18], C_8H_8 [81] or $C_{10}H_{12}$ [18]).

Such ligands can also displace ethylene, which is more weakly bound.

$$[C_2H_4PtCl_2]_2 + 2\,olen \rightarrow 2\,[olenPtCl_2] + 2\,C_2H_4$$
(olen = C_4H_6 [62], C_7H_8 [76] or $C_{10}H_{16}$ [77])
$$H[C_2H_4PtCl_3] + nor\text{-}C_7H_8 \rightarrow [nor\text{-}C_7H_8PtCl_2] + C_2H_4 + HCl$$

In certain cases, CO groups can be displaced by di- or oligo-olefins even more easily.

$$[Rh(CO)_2Cl]_2 + 2\,olen \rightarrow [olenRhCl]_2 + 4\,CO$$
(olen = 1,5-C_8H_{12} [19] or C_8H_8 [19])
$$Pd(CO)Cl_2 + olen \rightarrow [olenPdCl_2] + CO$$
(olen = nor-C_7H_8, 1,5-C_8H_{12} or $C_{18}H_{24}$ [82]).

2. $(olen)_mMeX_nL$

In polynuclear di- and oligo-olefin-metal halides of formula $[olenRhCl]_2$, where olen = nor-C_7H_8 [58], C_8H_8 [58], 1,5-C_8H_{12} [16, 19], or $C_{10}H_{12}$ [19], and $[olenRuCl_2]_n$, where olen = nor-C_7H_8 [58], C_8H_8 [59], or 1,5-C_8H_{12} [59], the halogen bridges can be broken easily by treatment with neutral ligands with strong donor characteristics, *e.g.* amines, phosphines, arsines, or stibines. The coordination numbers are unchanged in this process.

$$[nor\text{-}C_7H_8RhCl]_2 + 2\,L \rightarrow 2\,[nor\text{-}C_7H_8RhClL]$$
(L = *p*-tol, $P(C_6H_5)_3$, $(C_6H_5)_2PCH_3$, $As(C_6H_5)_3$ or $Sb(C_6H_5)_3$] [83])
$$[nor\text{-}C_7H_8RuCl_2]_n + 2n\,p\text{-tol} \rightarrow n\,[nor\text{-}C_7H_8(p\text{-tol})_2RuCl_2]\ [58]$$

3. $(olen)_mMe(CO)_n$

To prepare these compounds, the starting materials are usually metal carbonyls. *Reihlen* and co-workers [7] obtained butadieneiron tricarbonyl in a sealed tube, using quite drastic conditions:

$$C_4H_6 + Fe(CO)_5 \rightarrow C_4H_6Fe(CO)_3 + 2\,CO$$

This method has meanwhile been applied to the preparation of analogous $[olenFe(CO)_3]$ complexes, *e.g.* with 1,3-C_6H_8 [20], 1,3-C_6F_8 [84, 85], 1,3-C_7H_{10} [86], 1,5-C_8H_{12} [86], 1,5,9-$C_{12}H_{18}$ [86], substituted cyclopentadienones [87], or thiophene dioxides [87].

Di- and oligo-olefins also react with metal carbonyls under normal pressure. The carbon monoxide evolved can then escape unimpeded, and the equilibrium shifts in favor of the substitution product.

$$m\,olen + Me(CO)_x \rightleftharpoons (olen)_mMe(CO)_n + (x-n)\,CO$$

High-boiling hydrocarbons have been found effective as solvents, since in most cases the reaction starts only at high temperatures. In this fashion, the following compounds were obtained:

[75] *G. G. Koblyanskiy, A. A. Shul'ts,* and *K. B. Piotrovskiy,* Trudy Gosudarst. Opyt. Zavoda Sintet. Kauchuka *1935,* 20.

[76] *R. A. Alexander, N. C. Baenziger, C. Carpenter,* and *J. R. Doyle,* J. Amer. chem. Soc. *82,* 535 (1960).

[77] *J. Chatt* and *R. G. Wilkins,* J. chem. Soc. (London) *1952,* 2622.

[78] *G. Stölzle,* Ph.D. Thesis, Universität München, 1961.

[79] *T. L. V. Ulbricht,* Chem. and Ind. *1961,* 1570.

[80] *M. S. Kharasch, R. C. Seyler,* and *F. R. Mayo,* J. Amer. chem. Soc. *60,* 882 (1938).

[81] *H. P. Fritz* and *H. Keller,* Chem. Ber. *95,* 158 (1962).

[82] *E. O. Fischer* and *H. Werner,* Chem. Ber. *93,* 2075 (1960).

[83] *M. A. Bennet* and *G. Wilkinson,* J. chem. Soc. (London) *9161,* 1418.

[84] *K. F. Watterson* and *G. Wilkinson,* Chem. and Ind. *1959,* 991.

[85] *H. H. Hoehn, L. Pratt, K. F. Watterson,* and *G. Wilkinson,* J. chem. Soc. (London) *1961,* 2738.

[86] *W. Fröhlich,* Ph. D. Thesis, Universität München, 1961.

[87] *E. Weiss* and *W. Hübel,* J. inorg. nuclear Chem. *11,* 42 (1959).

[88] *A. Nakamura* and *N. Hagihara,* J. chem. Soc. Japan, pure Chem. Sect. (Nippon Kakagu Zassi) *82,* 1387 (1961).

[89] *R. B. King, T. A. Manuel,* and *F. G. A. Stone,* J. inorg. nuclear Chem. *16,* 233 (1961).

[90] *R. Burton, M. L. H. Green, E. W. Abel,* and *G. Wilkinson,* Chem. and Ind. *1958,* 1592.

[91] *R. Pettit,* J. Amer. chem. Soc. *81,* 1266 (1959).

[92] *C. W. Bird, R. C. Cookson,* and *J. Hudec,* Chem. and Ind. *1960,* 20.

[93] *M. L. H. Green, L. Pratt,* and *G. Wilkinson,* J. chem. Soc. (London) *1960,* 989.

[94] *R. Burton, L. Pratt,* and *G. Wilkinson,* J. chem. Soc. (London) *1961,* 594.

[95] *W. Hübel* and *E. Weiss,* Chem. and Ind. *1959,* 703.

[96] *E. Weiss* and *W. Hübel,* Chem. Ber. *95,* 1179 (1962).

[97] *H. J. Dauben Jr.* and *D. J. Bertelli,* J. Amer. chem. Soc. *83,* 497 (1961).

[98] *T. A. Manuel* and *F. G. A. Stone,* Chem. and Ind. *1960,* 231.

[99] *T. A. Manuel* and *F. G. A. Stone,* J. Amer. chem. Soc. *82,* 366 (1960).

[100] *T. A. Manuel* and *F. G. A. Stone,* J. Amer. chem. Soc. *82,* 6240 (1960).

[101] *R. B. King* and *F. G. A. Stone,* J. Amer. chem. Soc. *82,* 4575 (1960).

[102] *G. Bürger,* Ph. D. Thesis, Universität München, 1962.

olenFe(CO)$_3$: olen = 1,3-dihydromesitylene [89],
nor-C_7H_8 [90–93]
C_7H_8 [90, 94]
tropone [95, 96]
1,3-C_7H_{10} [97]
1,5-C_8H_{12} [89, 98]
C_8H_8 [23–25, 99],
bicyclo[4.2.0]-2,4-octadiene [28, 100]
1,3,5-cyclo-octatriene [100]
bicyclo[4.3.0]nonatriene [101]
1-vinyl-3-cyclohexene [102]
isoprene [89]
1,4-diphenylbutadiene [103, 104]
1,3-pentadiene [89]
substituted 1,3-pentadienes [89]
1,3,5-hexatriene [105]
2,6-dimethyl-2,4,6-octatriene [89]
substituted cyclopentadienones [87, 106, 107]
pentaphenylphosphole [108, 109].

olenFe_2(CO)$_6$: olen = C_8H_8 [23–25, 99]
vinylcycloheptatriene [110]
m- and *p*-divinylbenzene [104]
acenaphthylene [101].

(olen)$_2Co_2$(CO)$_4$: olen = C_4H_6 [111]
isoprene [112]
2,3-dimethylbutadiene [113]
1,3-C_6H_8 [113, 114]
nor-C_7H_8 [113, 114]
C_8H_{10} [27].

olenCo_2(CO)$_6$: olen = 2,3-dimethylbutadiene [113]
nor-C_7H_8 [113, 114].

olenMe(CO)$_3$: Me = Cr, Mo or W
olen = C_7H_8 [22, 115–117]
substituted cycloheptatrienes [115, 116]
C_8H_{10} [26, 28]
5,6-dimethylenebicyclo[2.2.1]-2-heptene [110]
bicyclo[4.3.0]nonatriene [101, 118].

olenMe(CO)$_4$: Me = Cr, Mo or W
olen = nor-C_7H_8 [91, 116]
1,5-C_8H_{12} [59, 116, 119, 120]
dimethyldivinylsilane [98]
bicyclo[2.2.3]-2,5-octadiene [116].

(olen)$_2$Me(CO)$_2$: Me = Mo or W
olen = C_4H_6 [121]
1,3-C_6H_8 [122]
C_8H_{10} [26, 28]
tetraphenylcyclopentadienone [87].

Irradiation with ultraviolet light has also proved useful for the reaction of di- and oligo-olefins with metal carbonyls. The explanation of the course of this photochemical substitution reaction is due principally to *Strohmeier* and co-workers [123, 124]. By absorption of a quantum of light, the metal carbonyl is converted into an excited particle, which is short-lived and which decomposes with ejection of a CO group. The reactive, CO-deficient radical thus formed contains a coordination gap, which an olefin can fill with formation of a π-bond. Since the carbonyl residue which is eliminated can also serve as a donor, it is advisable to use an excess of the olefinic ligand and to remove the carbon monoxide from the reaction phase.

Acceleration of the reaction by irradiation offers advantages in many cases. It is of utmost importance that the reaction temperature be kept low by choice of a suitable solvent. Polymerization of the olefinic system can also be suppressed. Examples of substances prepared in this manner are $C_6H_8Fe(CO)_3$ [49], 1,5-$C_8H_{12}Fe(CO)_3$ [89], $C_8H_8Fe(CO)_3$ [24, 25], $C_8H_8Fe_2(CO)_6$ [24, 25] $C_8H_7FeC_6H_5(CO)_3$ [88], $C_8H_7Fe_2C_6H_5(CO)_6$ [88], isopreneFe(CO)$_3$ [89], 1,2,3,4-tetraphenylbutadieneFe(CO)$_3$ [107], $(C_4H_6)_2Co_2(CO)_4$ [111], and $(C_4H_6)_2Mo(CO)_2$ [121].

Some di- and oligo-olefin-metal carbonyls can also be obtained by ligand exchange. Cycloheptatrienetungsten tricarbonyl for example, is accessible in very good yield [98] by the reaction:

$$C_8H_{12}W(CO)_4 + C_7H_8 \rightarrow C_7H_8W(CO)_3 + C_8H_{12} + CO$$

Diolefins such as butadiene or 1,3-cyclohexadiene likewise displace six-membered aromatic rings; thus, *e.g.* $C_6H_3(CH_3)_3Me(CO)_3$ plus 1,3-C_6H_8 yield $(C_6H_8)_2Me(CO)_2$, where Me = Cr or Mo [45], and $C_6H_3(CH_3)_3Mo(CO)_3$ plus C_4H_6 yields $(C_4H_6)_2Mo(CO)_2$ [45, 121].

Numerous di- and oligo-olefin-metal carbonyl compounds have been prepared from metal carbonyls and alkynes, principally by *Reppe* and later by *Hübel*; *e.g.* with tetraphenylcyclobutadiene, cyclopentadienone, substituted cyclopentadienones, duroquinone, and tropone as ligands. The kind of ligand system formed depends on the alkyne component. The first step of this reaction, which is induced by heat or irradiation, probably involves formation of unstable, reactive carbonyl fragments, which then react further with the alkyne. In most cases, the CO present in the reaction zone as a result of the decomposition of the metal carbonyl is incorporated as a keto group into the olefinic rings which are formed.

4. (olen)$_m$Me(CO)$_{n-1}$ L

In some cases, substitution of a CO group by ligands of strong donor character is possible in compounds of the type (olen)$_m$Me(CO)$_n$. Thus, the preparation of (di-

[103] *M. Cais* and *M. Feldkimel*, Tetrahedron Letters *1961*, No. 13, 444.
[104] *T. A. Manuel, S. L. Stafford*, and *F. G. A. Stone*, J. Amer. chem. Soc. *83*, 3597 (1961).
[105] *J. Xavier, M. Thiel*, and *E. R. Lippincott*, J. Amer. chem. Soc. *83*, 2403 (1961).
[106] *G. N. Schrauzer*, Chem. and Ind. *1958*, 1403.
[107] *G. N. Schrauzer*, J. Amer. chem. Soc. *81*, 5307 (1959).
[108] *E. H. Braye* and *W. Hübel*, Chem. and Ind. *1959*, 1250.
[109] *E. H. Braye, W. Hübel*, and *J. Caplier*, J. Amer. chem. Soc. *83*, 4406 (1961).
[110] *R. B. King* and *F. G. A. Stone*, J. Amer. chem. Soc. *83*, 3590 (1961).
[111] *E. O. Fischer, P. Kuzel*, and *H. P. Fritz*, Z. Naturforsch. *16b*, 138 (1961).
[112] *P. Kuzel*, Ph.D. Thesis, Universität München, 1962.
[113] *G. Winkhaus* and *G. Wilkinson*, J. chem. Soc. (London) *1961*, 602.
[114] *G. Winkhaus* and *G. Wilkinson*, Chem. and Ind. *1960*, 1083.
[115] *E. W. Abel, M. A. Bennet, R. Burton*, and *G. Wilkinson*, J. chem. Soc. (London) *1958*, 4559.
[116] *M. A. Bennet, L. Pratt*, and *G. Wilkinson*, J. chem. Soc. (London) *1961*, 2037.
[117] *W. Strohmeier*, Chem. Ber. *94*, 2490 (1961).
[118] *R. B. King* u. *F. G. A. Stone*, Chem. and Ind. *1960*, 232.
[119] *E. O. Fischer* and *W. Fröhlich*, Chem. Ber. *92*, 2995 (1959).
[120] *T. A. Manuel* and *F. G. A. Stone*, Chem. and Ind. *1959*, 1349.
[121] *E. O. Fischer, H. P. Kögler*, and *P. Kuzel*, Chem. Ber. *93*, 3006 (1960).
[122] *E. O. Fischer* and *W. Fröhlich*, Z. Naturforsch. *15b*, 266 (1960).
[123] *W. Strohmeier* and *K. Gerlach*, Chem. Ber. *94*, 398 (1961).
[124] *W. Strohmeier* and *D. v. Hobe*, Chem. Ber. *94*, 761 (1961).

carbonyl)tetraphenylcyclopentadienoneiron triphenylphosphine or triphenylphosphite [87] proceeds in good yield:

$$[C_5(C_6H_5)_4O]Fe(CO)_3 + PR_3 \rightarrow [C_5(C_6H_5)_4O]Fe(CO)_2PR_3 + CO$$
$$(R = C_6H_5 \text{ or } OC_6H_5)$$

as does that of (dicarbonyl) cyclo-octatetraeneiron triphenylarsine or triphenylstibine [99]:

$$C_8H_8Fe(CO)_3 + M(C_6H_5)_3 \rightarrow C_8H_8Fe(CO)_2M(C_6H_5)_3 + CO$$
$$(M = As \text{ or } Sb)$$

5. (dien)$MeC_5H_5(CO)_n$

Neutral diolefin-cyclopentadienyl-metal carbonyls of V, Mn, and Re are known. Thus, $C_5H_6ReC_5H_5(CO)_2$ [125, 126] was obtained indirectly by treatment of $(C_5H_5)_2$-ReH with CO under pressure, while the vanadium and manganese complexes are accessible by the reaction of diolefins with the corresponding cyclopentadienyl-metal carbonyl. $C_5H_5V(CO)_4$ always reacts in this manner.

$$C_5H_5V(CO)_4 + dien \rightarrow dienVC_5H_5(CO)_2 + 2\ CO$$
(dien = C_4H_6, 2,3-dimethylbutadiene or 1,3-C_6H_8) [121]

On the other hand, three possibilities occur in the substitution of $C_5H_5Mn(CO)_3$:

a) $C_5H_5Mn(CO)_3 + dien \rightarrow dienMnC_5H_5(CO) + 2\ CO$
(dien = C_4H_6 [121])

b) $C_5H_5Mn(CO)_3 + dien \rightarrow dienMnC_5H_5(CO)_2 + CO$
(dien = 1,3-C_6H_8 [127], nor-C_7H_8 [45], $C_{10}H_{12}$ [45])

c) $2\ C_5H_5Mn(CO)_3 + dien \rightarrow dien[C_5H_5Mn(CO)_2]_2 + 2\ CO$
(dien = 1,3-C_6H_8 [127] or 1,5-C_8H_{12} [45]).

Which of the products is obtained depends both on the diolefin and particularly on the reaction conditions.

The preparation of cationic diolefin-cyclopentadienyl-iron dicarbonyls has been accomplished in the authors' laboratory. Here, a coordination gap was created by removal of a σ-bonded ligand such as a halogen; this gap can then be filled by an olefin with formation of a π-bond [128].

$$C_5H_5Fe(CO)_2Br + dien \xrightarrow{AC} [dienFeC_5H_5(CO)_2]^+ + Br^-$$
(dien = C_4H_6 or 1,3-C_6H_8; AC = acceptor such as $ZnCl_2$ or $AlCl_3$) [129]

6. (olen)Me(aromatic)

This group contains the di- and oligo-olefin-metal cyclopentadienyls of Co and Rh, as well as the diene-benzene-metal complexes $C_6H_8RuC_6H_6$ [56] and $C_6H_8FeC_6H_6$ [56a]. A coordination number of 5 for the central atom and a filled electron shell are common to all of these compounds; both features are certainly responsible for the remarkable stability observed.

The following methods of preparation have been used:

a) Reaction of anhydrous metal halides in polar solvents, such as tetrahydrofuran or ethylene glycol dimethyl ether, with a cyclopentadienylalkali and excess diolefin (preparation of $C_5H_5RhC_5H_6$ and $C_5H_5IrC_5H_6$ [29, 30]).

b) Action of a di- or oligo-olefin on cyclopentadienyl-cobalt dicarbonyl:

$$C_5H_5Co(CO)_2 + olen \rightarrow C_5H_5Co(olen) + 2\ CO$$
(olen = 2,3-dimethylbutadiene [86], 1,3-C_6H_8 [86, 130], nor-C_7H_8 [130], 1,5-C_8H_{12} [130—132], bicyclo[4.2.0]-2,4-octadiene [130] or C_8H_8 [131, 133])

Ultraviolet irradiation is often useful for obtaining good yields. Alkynes, such as $C_2(C_6H_5)_2$ or $C_2(CH_3)_2$, likewise react with $C_5H_5Co(CO)_2$, leading to cyclopentadienylcobalt cyclopentadienones [134]. In similar fashion $C_5H_5Rh(CO)_2$ and 2,3-dimethylbutadiene yield $C_5H_5RhC_6H_{10}$ [134a].

c) Reaction of a dimeric diolefin-metal halide with a cyclopentadienylalkali:

$$[C_8H_{12}RhCl]_2 + 2\ NaC_5H_5 \rightarrow 2\ C_5H_5RhC_8H_{12} + 2\ NaCl\ [16, 19]$$

d) Reduction of diaromatic-metal cations with $NaBH_4$ [31], $LiAlH_4$ [31], or sodium amalgam [53], whereby a cyclopentadienyl residue is converted into a cyclopentadiene residue.

$$[Me(C_5H_5)_2]^+ + H^- \rightarrow C_5H_5MeC_5H_6 \quad (Me = Co \text{ or } Rh)$$

Similarly, $C_5H_4CH_3CoC_5H_5CH_3$ [31] has been prepared from $[Co(C_5H_4CH_3)_2]^+$, and $C_6H_8RuC_6H_6$ [56] from $[Ru(C_6H_6)_2]^{2+}$.

1-*endo*-Substituted cyclopentadiene complexes are formed by nucleophilic addition of aryl lithium or alkyl lithium or Grignard compounds onto the cation $[Co(C_5H_5)_2]^+$ [135].

e) Metal cyclopentadienyls, such as $Co(C_5H_5)_2$, react with alkyl or acyl halides, also yielding diolefin-cyclopentadienyl-metal compounds.

$$2\ Co^{II}(C_5H_5)_2 + RX \rightarrow [Co^{III}(C_5H_5)_2]X + (1\text{-}endo\text{-}RC_5H_5)Co^{I}C_5H_5$$
(RX = CCl_4 [31, 136], CH_3I [31], CF_3I [31] or C_6H_5COCl [135]).

7. (olen)$_m$Me

So far, uncharged olefin-metal complexes have been described only in the case of nickel. The $NiC_{12}H_{18}$ [137], prepared from nickel acetylacetonate and 1,5,9-cyclo-do-

[125] *E. O. Fischer* and *A. Wirzmüller*, Z. Naturforsch. *12b*, 737 (1957).

[126] See *M. L. H. Green* and *G. Wilkinson*, J. chem. Soc. (London) *1958*, 4314.

[127] *E. O. Fischer* and *M. Herberhold*, Z. Naturforsch. *16b*, 841 (1961).

[128] *E. O. Fischer* and *K. Fichtel*, Chem. Ber. *94*, 1200 (1961).

[129] *K. Fichtel*, Ph.D. Thesis, Universität München, 1961.

[130] *R. B. King*, *P. M. Treichel*, and *F. G. A. Stone*, J. Amer. chem. Soc. *83*, 3593 (1961).

[131] *A. Nakamura* and *N. Hagihara*, Bull. chem. Soc. Japan *33*, 425 (1960).

[132] *A. Nakamura* and *N. Hagihara*, Bull. chem. Soc. Japan *34*, 452 (1961).

[133] *H. P. Fritz* and *H. Keller*, Z. Naturforsch. *16b*, 348 (1961).

[134] *R. Markby*, *H. W. Sternberg*, and *I. Wender*, Chem. and Ind. *1959*, 1381.

[134a] *K. Bittler*, Ph.D. Thesis, Technische Hochschule München, 1962.

[135] *E. O. Fischer* and *G. E. Herberich*, Chem. Ber. *94*, 1517 (1961).

[136] *S. Katz*, *J. F. Weiher*, and *A. F. Voigt*, J. Amer. chem. Soc. *80*, 6459 (1958).

[137] *G. Wilke*, Angew. Chem. *72*, 581 (1960).

decatriene with *Ziegler* catalysts, is used to prepare bis-(1,5-cyclo-octadiene)nickel(0) and probably polymeric cyclo-octatetraene-nickel(0).

$$NiC_{12}H_{18} + m\ olen \rightarrow Ni(olen)_m + C_{12}H_{18}$$
(olen = 1,5-C_8H_{12} or C_8H_8; m = 1 or 2 [137])

Substitution of the CO groups in $Ni(CO)_4$ is possible only with tetraphenylcyclopentadienone [87], duroquinone [51, 138], or a mixture of duroquinone and an oligo-olefin, *e.g.* nor-C_7H_8 [139], 1,5-C_8H_{12} [139], C_8H_8 [138], or $C_{10}H_{12}$ [139].

$$Ni(CO)_4 + 2\ olen \rightarrow Ni(olen)_2 + 4\ CO$$

Preparative Results

The di- and oligo-olefin-metal complexes so far described are summarized in Table 1. Review of the individual compounds in this article would be unnecessarily lengthy. A survey of some especially pertinent portions of the subject is therefore given below [*].

Table 1. Di- and oligo-olefin-metal complexes described up to the present.

	V	Cr	Mo	W	Mn	Re	Fe	Ru	Co	Rh	Ir	Ni	Pd	Pt	Ag	Cu
Cyclobutadiene							+		+			+	+		+	
Cyclopentadiene						+	+		+	+	+				+	
Cyclopentadienone			+				+		+			+				
Heterocyclic dienes							+									
Cyclohexadiene	+	+	+		+		+	+	+						+	
Duroquinone							+					+				
Norbornadiene		+	+	+	+		+	+	+	+		+	+	+	+	+
Cycloheptatriene		+	+	+			+							+		
Cycloheptadiene							+									
Cyclo-octatetraene			+				+	+	+	+		+	+	+	+	+
Cyclo-octadiene		+	+	+	+		+	+	+	+		+	+	+	+	+
Ligands of formula C_8H_{10}		+	+	+			+		+						+	
Ligands of formula C_9H_{10}		+	+	+			+									
Divinylbenzene							+									
Vinylcyclohexane							+									
Cyclododecatriene							+					+				
Acenaphthylene		+					+									
Dipentene														+		
Dicyclopentadiene					+	+				+		+	+	+	+	+
Butadiene	+		+		+		+		+	+				+		+
Pentadiene							+									
Hexadiene				+			+						+	+	+	
Hexatriene							+									
Octatriene							+									

1. Metal π-Complexes with Cyclobutadiene Ligands

The prediction of *Longuet-Higgins* and *Orgel* [140], that cyclobutadiene, which had hitherto been sought unsuccessfully, could be stabilized by complex formation, was confirmed three years later by the discovery of C_4R_4 complexes of iron, nickel, and silver. The preparation of these complexes is extraordinary: $C_4(C_6H_5)_4Fe(CO)_3$ is formed, together with numerous other Fe complexes, by the action of diphenylacetylene on iron carbonyls [35]; $C_4(CH_3)_4NiCl_2$ is obtained from 1,2-dichlorotetramethylcyclobutene and $Ni(CO)_4$ in boiling benzene or ether [32, 33], and $[C_4H_4Ag]NO_3$ by shaking an ether solution obtained from 1,2,3,4-tetrabromocyclobutene plus Li/Hg with saturated aqueous $AgNO_3$ [34].

X-ray investigations indicate a planar, symmetrical four-membered ring in both $C_4(C_6H_5)_4Fe(CO)_3$ [141] and $C_4(CH_3)_4NiCl_2$ [142, 143]. The latter compound is dimeric in the crystal lattice *(7)*: every nickel atom is bound to the cyclobutadiene ring and to three chlorine atoms, two of which, together with the second nickel atom, form a four-membered ring. The methyl groups do not lie exactly in the plane of the C_4 ring, a fact attributed to steric interaction with the chlorine atoms [143].

[138] *G. N. Schrauzer* and *H. Thyret*, Z. Naturforsch. *16b*, 353 (1961).

[139] *G.N. Schrauzer* and *H. Thyret*, Z. Naturforsch. *17b*, 73 (1962).

[*] A comprehensive literature compilation is provided in a monograph by *E. O. Fischer* and *H. Werner*: "Metall-π-Komplexe mit di- und oligo-olefinischen Liganden", to be published shortly by Verlag Chemie.

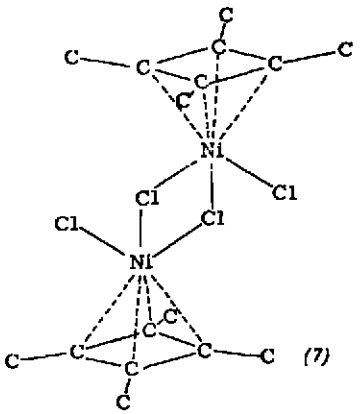
[140] *H. C. Longuet-Higgins* and *L. E. Orgel*, J. chem. Soc. (London) *1956*, 1969.

[141] *R. P. Dodge* and *V. Schomaker*, Nature (London) *186*, 798 (1960).

[142] *J. D. Dunitz, H. C. Mez, O. S. Mills, P. Pauling*, and *H. M. M. Shearer*, Angew. Chem. *72*, 755 (1960).

[143] *J. D. Dunitz, H. C. Mez, O. S. Mills*, and *H. M. M. Shearer*, Helv. chim. Acta *45*, 647 (1962).

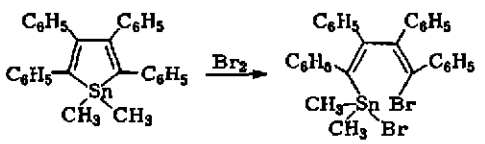
The spectra of the complexes $C_4(C_6H_5)_4Fe(CO)_3$, $C_4(CH_3)_4NiCl_2$, $C_4(C_6H_4Cl)_4Fe(CO)_3$ [144], and $C_4(C_6H_5)_4NiCl_2$ [144], as well as $C_4(C_6H_5)_4PdCl_2$, which is obtained from $[(C_6H_5CN)_2PdCl_2]$ [145] or $PdCl_2$ [145, 146] and $C_2(C_6H_5)_2$, agree with their symmetrical structure. The



(7)

infrared spectra [147] are relatively devoid of bands and are similar when the ligands are alike. According to nuclear magnetic resonance measurements [148], a monomeric C_4 ring is also present in $[C_4H_4Ag]NO_3$. The NMR spectrum of this substance in a saturated solution of $AgClO_4$ in D_2O shows only one sharp signal, which occurs at extremely low field ($\tau = 2.7$) and which is ascribed to a strained, conjugated ring system.

The blue-black, thermally stable $C_4(C_6H_5)_4NiBr_2$ [149] *(10)* deserves mention here because of its original synthesis.



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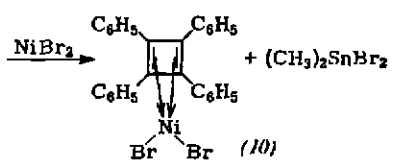
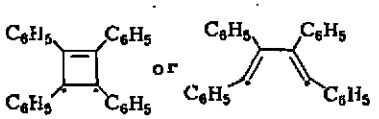


(10)

On decomposition of substance *(9)*, the solution becomes green, suggesting the occurrence of a diradical *(11)* [149], such as is also required for the ground state of cyclobutadiene.



(11)

C_4R_4-Co complexes of composition $C_5H_5CoC_4(C_6H_5)_4$ [132], $[Co_4Hg_2(CO)_{12}(C_4(C_6H_5)_2H_2)]$ [150], $[Co_6Hg_3(CO)_{16}(C_4(C_6H_5)_2H_2)_2]$ [150], and $[Co_2Hg(CO)_4(C_4(C_6H_5)_2H_2)]_n$ [150] have been prepared from $C_5H_5CoC_8H_8$ or $Hg[Co(CO)_4]_2$ and alkynes.

[144] *W. Hübel* et al., unpublished.

[145] *A. T. Blomquist*, 141st Meeting Amer. chem. Soc., Washington, March 1962, Abstracts p. 25–0.

[146] *L. Malatesta, G. Santarella, L. Vallarino*, and *F. Zingales*, Angew. Chem. *72*, 34 (1960).

[147] *H. P. Fritz*, Z. Naturforsch. *16b*, 415 (1961).

[148] *H. Keller*, Ph.D. Thesis, Universität München, 1962.

[149] *H. H. Freedman*, J. Amer. chem. Soc. *83*, 2194, 2195 (1961).

[150] *U. Krüerke* and *W. Hübel*, Chem. Ber. *94*, 2829 (1961).

2. Metal π-Complexes with Cyclohexadiene and Cyclohexadienyl Ligands

Attempts to replace CO groups in metal carbonyls and aromatic-metal carbonyls with 1,3-cyclohexadiene have been successful in many instances. The first Me-CO complex of a cyclic diolefin, $C_6H_8Fe(CO)_3$ [20] was followed by $(C_6H_8)_2Cr(CO)_2$ [45], $(C_6H_8)_2Mo(CO)_2$ [45, 122], $[C_6H_8Co(CO)_2]_n$ [86, 113], where n = 1 or 2, $C_6H_8CoC_5H_5$ [86, 130], $C_6H_8VC_5H_5(CO)_2$ [121], $C_6H_8MnC_5H_5(CO)_2$ [127], and $C_6H_8[C_5H_5Mn(CO)_2]_2$ [127]. According to NMR measurements [145], all of these complexes contain the 1,3-C_6H_8 in the unchanged diene configuration. Cyclohexadiene is thus different from cyclopentadiene, which reacts with metal carbonyls to form not diene, but aromatic (*i.e.*, cyclopentadienyl) complexes. In spite of numerous attempts, it has not been possible to obtain a $C_5H_6Fe(CO)_3$ by a reaction between $Fe(CO)_5$ and C_5H_6; instead $[C_5H_5Fe(CO)_2]_2$ is always produced [151]. This tendency towards symmetrization in cyclopentadiene is also shown in the preparation of such compounds as $NiC_{10}H_{12}$ [152] or $C_{10}H_{12}Cr(CO)_2$ [153], in which not two diene ligands, but rather one dienyl and one enyl are coordinated with the central atom ($C_5H_5NiC_5H_7$ [154] or $C_5H_5CrC_5H_7(CO)_2$ [155]). Such a disproportionation

$$2\,C_5H_6 \rightarrow C_5H_5 + C_5H_7$$

has not yet been observed with cyclohexadiene. The compounds $(C_6H_8)_2Cr(CO)_2$ and $(C_6H_8)_2Mo(CO)_2$ mentioned above are bis(cyclohexadiene) complexes and not cyclohexadienylcyclohexenyl complexes [45].

The C_6H_7 residue can nevertheless appear as a ligand. In 1960, *Winkhaus* and *Wilkinson* obtained a yellow compound $C_6H_7Mn(CO)_3$ (which was stable in air) by the reaction of $Mn_2(CO)_{10}$ with 1,3-C_6H_8 [156]. In the same year, the preparation of the isoelectronic cation $[C_6H_7Fe(CO)_3]^+$ was achieved [157] in the authors' laboratory by elimination of hydride from $C_6H_8Fe(CO)_3$. Cyclohexadienylmanganese tricarbonyl is even more readily obtainable by reduction of $[C_6H_6Mn(CO)_3]^+$ with $NaBH_4$ in aqueous solution, or with $LiAlH_4$ in ether [156, 158].

$$[C_6H_6Mn(CO)_3]^+ \underset{-H^-}{\overset{+H^-}{\rightleftharpoons}} C_6H_7Mn(CO)_3$$

A reverse reaction occurs with CCl_4 or other hydride-abstracting compounds such as trityl tetrafluoroborate. The case of cleavage of a C–H bond in this system is certainly due to steric interaction of a hydrogen atom (H^{α}) with the metal. Correspondingly, one finds a rather long-wave CH valence vibration at *ca.* 2810 cm^{-1} in the infrared spectrum of

[151] See *P. L. Pauson*, Proc. chem. Soc. (London) *1960*, 297.

[152] *E. O. Fischer* and *H. Werner*, Chem. Ber. *92*, 1423 (1959).

[153] *E. O. Fischer* and *K. Ulm*, Z. Naturforsch. *15b*, 59 (1960).

[154] *E. O. Fischer* and *H. Werner*, Tetrahedron Letters *1961*, No. 1, 17; *M. Dubeck* and *A. H. Filbey*, J. Amer. chem. Soc. *83*, 1257 (1961); *D. Jones, G. W. Parshall, L. Pratt*, and *G. Wilkinson*, Tetrahedron Letters *1961*, No. 2, 48.

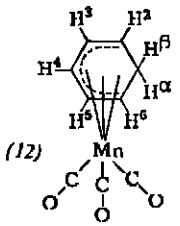
[155] *E. O. Fischer* and *K. Ulm*, Chem. Ber. *94*, 2413 (1961).

[156] *G. Winkhaus* and *G. Wilkinson*, Proc. chem. Soc. (London) *1960*, 311.

[157] *E. O. Fischer* and *R. D. Fischer*, Angew. Chem. *72*, 919 (1960).

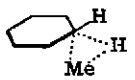
[158] *G. Winkhaus, L. Pratt*, and *G. Wilkinson*, J. chem. Soc. (London) *1961*, 3807.

$C_6H_7Mn(CO)_3$ [49, 158]. Furthermore, the occurrence of three ν-CO bands indicates a lower symmetry than that of $C_5H_5Mn(CO)_3$, so that free rotation of the organic ligands about the ring-metal axis is evidently no longer possible. The NMR spectrum in C_6H_6 is in agreement with this. It shows that the protons H^4, $H^{3,5}$, and $H^{2,6}$ [see *(12)*] are not equivalent, although approximtely the same π-electron density is assumed for carbon atoms C-2 to C-6. The signals of the methylene protons also are displaced by different amounts (H^β $\tau = 7.7$; H^α: $\tau = 8.44$), confirming their respective "*exo*"- and "*endo*"-positions relative to the metal. In the deuterium compound $C_6H_6DMn(CO)_3$, the H^α signal in the NMR spectrum and the C–H^α valence vibration in the infrared spectrum are absent [158].



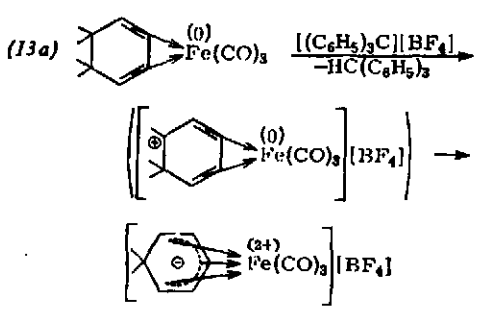
(12)

Substituted cyclohexadienylmanganese tricarbonyls are formed from the corresponding $[ArMn(CO)_3]^+$ cations (Ar = toluene, mesitylene, hexamethylbenzene, or naphthalene) by means of $NaBH_4$ [158]. The view has been expressed that here a metal-hydrogen bond is formed first, and only thereafter is a hydrogen atom transfered to the ring [158]. A structure of type *(13)* may exist as a transition state [49].



(13)

The $[C_6H_7Fe(CO)_3]^+$ cation [157], which is prepared similarly



and which is stable in aqueous solution, can be precipitated as its tetraphenylborate, perchlorate, or hexafluorophosphate. It reacts with nucleophilic agents $R^\ominus$ (R = H or CN) to form uncharged cyclohexadieneiron tricarbonyls [49].

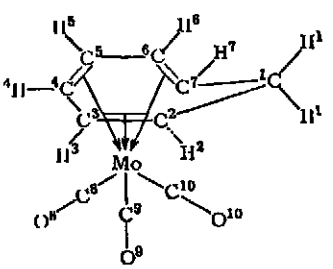
The cyclohexadienyl complexes $C_6H_7FeC_5H_5$ and $C_6H_7ReC_6H_6$ are obtained by reduction of the cations $[C_6H_6FeC_5H_5]^+$ and $[(C_6H_6)_2Re]^+$, respectively, with $LiAlH_4$ or $NaBH_4$ [56]. In contrast, with $NaBH_4$, $[(C_6H_6)_2Ru]^{2+}$ yields a green crystalline compound $C_6H_8RuC_6H_6$, which is judged on the basis of its NMR spectrum to be a dienebenzene complex and not $Ru(C_6H_7)_2$ [56]. The analogous orange-colored compound $C_6H_8FeC_6H_6$ is formed in a remarkable reaction by the simultaneous action of 1,3-C_6H_8 and an alkyl Grignard compound on a suspension in ether of $FeCl_3$ [159]. The tendency of 1,3-cyclohexadiene to aromatize, which exhibits itself here, becomes still stronger in a novel dibenzenechromium synthesis from $CrCl_3$, C_2H_5MgBr, and C_6H_8 [160].

Besides the cyclohexadienyl residue, the cyclohexenyl residue, C_6H_9, is also known as a ligand in metal π-complexes. For example, 1,3-C_6H_8 reacts with $Pd(CO)Cl_2$ to form a yellow crystalline material $[C_6H_9PdCl]_2$, further reaction of which with cyclopentadienylalkali leads to π-dienyl-π-enylpalladium compounds [82, 161]. The compound $C_6H_9PdC_5H_5$, is quite stable, is obtainable in yields of 80–90%, and can be used as starting material for the preparation of Pd(O) complexes such as $[(C_6H_5)_3P]_4Pd$, $(C_6H_{11}NC)_2Pd$, or $(iso\text{-}C_3H_7NC)_2Pd$ [162].

3. Metal π-Complexes with Cycloheptatriene and Cycloheptatrienyl Ligands

After the synthesis of metal π-complexes with symmetrical five- and six-membered rings, the way was clear for the preparation of analogous compounds with the cycloheptatrienyl or tropylium cation. Since initial experiments with C_7H_7 salts failed [163], the achievement of the objective by the reaction of free C_7H_8 with metal carbonyls or salts was attempted. At first, success was attained only in the preparation of an orange-colored, diamagnetic complex $[C_7H_7PtBr_2]_2$ from $PtBr_4$ and cycloheptatriene [164].

In contrast, the action of C_7H_8 on $Mo(CO)_6$, led to a red, diamagnetic product $C_7H_8Mo(CO)_3$ [22], *i.e.* a compound with a triene and not a symmetric cycloheptatrienyl *(14)* [47]. The six sp^2-hybridized carbon atoms of the ring in this compound lie practically in one plane, while the methylene group projects outwards; the three CO residues provide approximately trigonal symmetry in relation to the Mo-ring axis. The distance between C-2 and C-7 (2.52 Å) prohibits overlapping of the free p-orbitals of these carbon atoms, so that it is hardly justifiable, to consider the cycloheptatriene in $C_7H_8Mo(CO)_3$ as a "quasi-aromatic" system.



(14)

True cycloheptatrienyl compounds of composition $[C_7H_7Me(CO)_3]^+$ are obtainable in almost quantitative

[159] *E. O. Fischer* and *J. Müller*, Z. Naturforsch. *17b*, 776 (1962).

[160] *E. O. Fischer*, *J. Müller*, and *P. Kuzel*, Rev. Chim. (Bucarest), in the press.

[161] *E. O. Fischer* and *H. Werner*, Chem. Ber. 95, 695 (1962).

[162] *E. O. Fischer* and *H. Werner*, Chem. Ber. *95*, 703 (1962).

[163] *H. P. Fritz*, Ph.D. Thesis, Technische Hochschule München, 1958.

[164] *E. O. Fischer* and *H. P. Fritz*, Z. physik. Chem., N.F. *17*, 132 (1958).

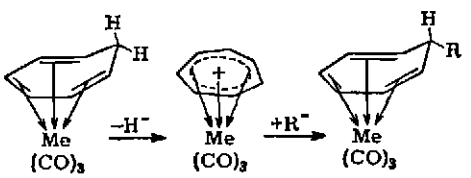
yields from either $C_7H_8Mo(CO)_3$ or the analogously prepared $C_7H_8Cr(CO)_3$ [115] by abstraction of hydride with trityl tetrafluoroborate [165–167]. The existence of a uniform C_7 ring is confirmed by NMR and infrared spectra [49,165,168]; in the former, only one sharp signal appears, while in the latter (as in $C_5H_5Mn(CO)_3$ and $C_6H_6Cr(CO)_3$), only two CO-valence vibrations are observed because of the increased symmetry.

The reactions of cations of the type $[C_7H_7Me(CO)_3]^+$ (Me = Cr or Mo) with nucleophilic agents can proceed along three paths:

1. Anions such as H^-, OCH_3^-, SH^-, I^-, diethyl methylmalonate, t-butylcyclopentadienyl, or monomethyl diethylmalonate in water, alcohol, or tetrahydrofuran add to the seven-membered ring [167,169]

$$[C_7H_7Me(CO)_3]^+ + X^- \rightarrow (C_7H_7X)Me(CO)_3 \text{ (Me = Cr or Mo)}$$

to effect substitution of the cycloheptatriene in $C_7H_8Me(CO)_3$ complexes via the intermediate cycloheptatrienyl compound *(15)* to give *(16)*.



(15) *(16)*

Compounds of the type $[C_7H_7Me(CO)_3]X$ are possibly intermediates, since, for example, in the reaction of KI on $[C_7H_7Cr(CO)_3]BF_4$ in tetrahydrofuran, a branching reaction was observed [49].

$$[C_7H_7Cr(CO)_3]BF_4 + KI \rightarrow \begin{cases} [C_7H_7Cr(CO)_3]I + KBF_4 & \text{(a)} \\ [C_7H_7I]Cr(CO)_3 + KBF_4 & \text{(b)} \end{cases}$$

Prolonged stirring favors the formation of the triene complex (b) from the salt-like $[C_7H_7Cr(CO)_3]I$ *via* nucleophilic addition. Since the infrared spectra of $(C_7H_7I)Cr(CO)_3$ and $(C_7H_7OCH_3)Cr(CO)_3$ show no long-wavelength CH valence vibration, the substituent must assume an "*endo*"-position relative to the central atom [49].

2. The reactions of cyclopentadienyl sodium or diethyl sodiomalonate with cations of the type $[C_7H_7Me(CO)_3]^+$ lead, surprisingly, to ring contraction [167,169].

$$[C_7H_7Me(CO)_3]^+ + C_5H_5^- \rightarrow C_6H_6Me(CO)_3 + C_6H_6 \text{ (Me = Cr or Mo)}$$

As tracer experiments have shown, the coordinatively bound six-membered ring always arises from the cycloheptatrienyl and not from the cyclopentadienyl residue. Intermediate formation of complexes $(C_7H_7R)Me(CO)_3$ with substituted cycloheptatriene ligands may also be assumed here; the CHR grouping is then split off [169].

3. Basic substances such as KCN, $NaHCO_3$, CH_3COONa, $NaNH_2$, C_6H_5Li, or benzamide also react "anomalously" with $[C_7H_7Cr(CO)_3]ClO_4$ [169]. The compounds isolated as main products, along with small amounts of $(C_7H_7R)Cr(CO)_3$, are dicycloheptatrienyl chromium tricarbonyl and dicycloheptatrienyl dichromium hexacarbonyl; these probably arise from the cycloheptatrienyl complex by reductive dimerization. A Cr(0) fragment initially formed could serve as reducing agent. The same transformation occurs with zinc dust [169].

$$2\,[C_7H_7Cr(CO)_3]^+ \rightarrow (OC)_3CrC_7H_7{-}C_7H_7Cr(CO)_3$$

The cycloheptatrienyl compounds of vanadium of formula $C_7H_7VC_5H_5$ [170] and $C_7H_7V(CO)_3$ [171] are obtainable from C_7H_8 and $C_5H_5V(CO)_4$ or $V(CO)_6$, respectively. While the structure of the purple-colored compound $C_7H_7VC_5H_5$ is not yet certain, the molecular configuration of the dark green, highly volatile complex $C_7H_7V(CO)_3$ has been determined by X-ray studies [172]. These show that the structure is typical of a "sandwich" molecule, with an approximately octahedrally coordinated metal atom; the plane of the C_7 ring lies parallel to that of the oxygen atoms, with V–O bond lengths of *ca.* 3.1 Å and V–C_{ring} bond lengths of *ca.* 2.3 Å. Thus, the cycloheptatrienylvanadium tricarbonyl becomes a member of the isoelectronic series $C_5H_5Mn(CO)_3$–$C_6H_6Cr(CO)_3$–$C_7H_7V(CO)_3$.

Only brief reference can be made here to the existence of Fe complexes with C_7H_8, C_7H_9, and C_7H_{10} as ligands. The most interesting facts are that the cycloheptadienyliron tricarbonyl cation $[C_7H_9Fe(CO)_3]^+$ is formed from $C_7H_8Fe(CO)_3$ by addition of a proton [94, 97], as well as from $C_7H_{10}Fe(CO)_3$ by hydride abstraction with trityl tetrafluoroborate [97].

4. Metal π-Complexes with Cyclo-octatetraene Ligands

Electron diffraction studies have established that the free hydrocarbon C_8H_8 has the boat form with D_{2d} symmetry [173]; in complexes, however, the eight-membered ring is bound to the central atom in various configurations. The unchanged boat form is present in the crystalline material $[C_8H_8Ag]NO_3$ [174]; each C_8H_8 molecule is firmly attached to an Ag^+ ion, and these $[C_8H_8Ag]^+$ units are arranged in rows along the c-axis of the crystal *(17)*. The average lengths of the C=C and C–C bonds are, 1.37 and 1.46 Å, respectively. The metal is not symmetrically located with respect to the four neighboring carbon atoms C-3, C-4, C-7, and C-8, since the Ag-C distances vary between 2.5 and 2.85 Å. It is possible that the π-electrons of the C-1 to C-2 and C-5 to C-6 bonds also interact with a silver atom of a neighboring chain, since no free C=C double

[165] *H. J. Dauben Jr.* and *L. R. Honnen*, J. Amer. chem. Soc. *80*, 5570 (1958).

[166] *H. J. Dauben Jr., L. R. Honnen, T. J. Pratt*, and *D. J. Bertelli*, 15th Southwest Regional Meeting, Amer. chem. Soc., Baton Rouge/La., Dec. 1959, Abstracts p. 89.

[167] *J. D. Munro* and *P. L. Pauson*, Proc. chem. Soc. (London) *1959*, 267.

[168] *H. P. Fritz*, habilitation thesis, Universität München, 1962.

[169] *J. D. Munro* and *P. L. Pauson*, J. chem. Soc. (London) *1961*, 3475.

[170] *R. B. King* and *F. G. A. Stone*, J. Amer. chem. Soc. *81*, 5263 (1959).

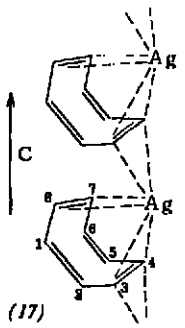
[171] *R. P. M. Werner* and *S. A. Manastyrskyj*, J. Amer. chem. Soc. *83*, 2023 (1961).

[172] *G. Allegra* and *G. Perego*, Ric. sci., Parte II *1A*, 362 (1961).

[173] *O. Bastiansen, L. Hedberg*, and *K. Hedberg*, J. chem. Physics *27*, 1311 (1957).

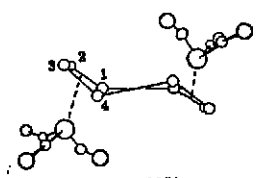
[174] *F. S. Mathews* and *W. N. Lipscomb*, J. Amer. chem. Soc. *80*, 4745 (1958).

bond bands are detected in the infrared spectrum and only one proton signal is observed in the NMR spectrum in benzonitrile or dimethyl sulfoxide [81]. The Ag-C_8H_8 bond is certainly strongly polar, since charge transfer bands are missing in the ultraviolet spectrum and Ag-ligand frequencies are absent in the far infrared [168].



(17)

The π-electron system of cyclo-octatetraene is certainly also involved in its bonding to the metal in $C_8H_8Fe_2(CO)_6$, but here the eight-membered ring assumes a chair form *(18)* [175]. Each $Fe(CO)_3$ group is bonded to an almost planar C_4H_4 fragment, in which, from a consideration of the sp^2 hybridized carbon atoms, the π-π overlap integral for C-2 and C-3 amounts to about 0.25, but only to about 0.11 for C-1 and C-2, and C-3 and C-4. In view of the bond lengths, interaction between the two halves of the C_8H_8 molecule can be assumed to be very small [175].

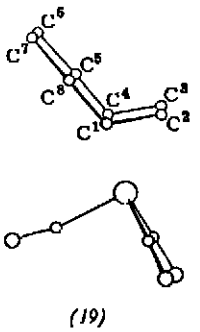


(18)

If $C_8H_8Fe_2(CO)_6$ is considered to be composed of two $-C_4H_4Fe(CO)_3-$ halves, the remarkable similarity of its infrared spectrum to that of $C_4H_6Fe(CO)_3$ becomes understandable [81]. The CO-valence, CC-valence, and CH-deformation vibrations have practically the same positions in both compounds. The NMR spectrum of $C_8H_8Fe_2(CO)_6$ contains two resonance lines at $\tau = 4.4$ and $\tau = 6.9$. The fairly shortwave ultraviolet maxima at 259 and 363 mμ are in agreement with the low mobility of the π-electrons in the "pseudo-butadiene structure" [81].

Extensive discussions followed the determination of the structure of $C_8H_8Fe(CO)_3$ by X-rays, according to which a hitherto unknown form is assigned to the C_8H_8 ligands *(19)* [176]. The $Fe(CO)_3$ group is bonded to only one half of the cyclo-octatetraene, while the remaining portion of the molecule lies in a plane inclined at an angle of 41 °. The overlap integrals for C-1 and C-5, and C-1 and C-8 (*ca.* 0.25) do not exclude interaction between the two halves of the ring [176].

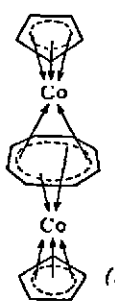
However, it is still difficult to reconcile the infrared and NMR spectra [81] with this structural picture *(19)*. There are no bands in the infrared spectrum which correspond in position and intensity to free, conjugated double bonds; in addition, of the eight infrared-active ν_{CH}-bands expected from C_s symmetry, at most only four are recognizable [177]. Furthermore, the NMR spectrum in such varied solvents as acetone, acetonitrile, benzene, $CHCl_3$, CCl_4, CS_2, cyclohexane, or pyridine [177] shows only one sharp signal, so that the same screening effect for all ring protons must be assumed. The form of the C_8H_8 ligand may possibly be altered in solution



(19)

owing to the release of the lattice forces, and this may explain these spectral observations. The various configurations may possibly interchange with relative ease. The form found in $C_8H_8Fe(CO)_3$ might then arise during the change of the boat into the chair form.

In the other C_8H_8 complexes prepared so far, the structure of the ring ligands is not yet known. In $C_8H_8PtI_2$ [73] and $C_8H_8PdCl_2$ [81], the eight-membered ring probably has the boat form as in $[C_8H_8Ag]NO_3$, with a completely delocalized π-electron system; the spectra of these compounds show only one proton signal and no valence vibrations of free double bonds [81]. A boat form of cyclo-octatetraene, in which only two C=C bonds in the 1- and 5-positions are coordinated with the central atom, is assumed for $(C_8H_8RhCl)_2$ [58], $C_8H_8 \cdot 2\,CuCl$ [63, 81], $C_8H_8CoC_5H_5$ [131, 133], and C_8H_8Ni (duroquinone) [138]. Two resonance lines in the NMR spectrum, as well as $\nu_{C=C}$ bands at about 1620 cm^{-1} in the infrared spectrum, are observed with these complexes. Indications as to the existence of a planar eight-membered ring have been found only in the compounds $K_2C_8H_8$ [81, 178] and $C_8H_8(CoC_5H_5)_2$ [81, 133]; the latter *(20)* is the first example of a highly symmetrical complex with a fourfold cone structure.



(20)

5. Metal π-Complexes with Butadiene Ligands

Just as diene, dienyl, and enyl compounds can be formed in the reactions of metal carbonyls and halides with 1,3-cyclohexadiene, varied and interesting types of complexes also arise in the reactions of butadiene. The historically significant compound $C_4H_6Fe(CO)_3$ [7, 20] is one of the metal compounds in which the C_4H_6 is present as an unchanged diene. Its structure *(21)*, as determined by X-rays [46], shows that the butadiene is bound in the *cis*-form; the four carbon atoms lie in one plane, which is, however, not parallel to the plane of the carbon atoms of the three CO groups. All the C–C distances of the hydrocarbon are identical, correspon-

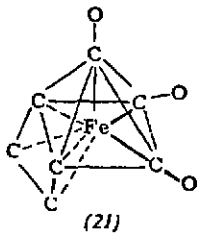
[175] *B. Dickens* and *W. N. Lipscomb*, J. Amer. chem. Soc. *83*, 489 (1961).

[176] *B. Dickens* and *W. N. Lipscomb*, J. Amer. chem. Soc. *83*, 4862 (1961).

[177] *H. P. Fritz*, Chem. Ber. *95*, 820 (1962).

[178] *H. P. Fritz* and *H. Keller*, Z. Naturforsch. *16b*, 231 (1961).

ding to complete delocalization of the π-electrons; at 1.45 to 1.46 Å, these distances are somewhat shorter than a single bond between two sp^2 carbon atoms. The magnitude of the C–C–C bond angle (118°) agrees with such a hybridization. The iron is equidistant from all four carbon atoms of the butadiene and is located about 0.2 Å above the base of the pyramid [46].

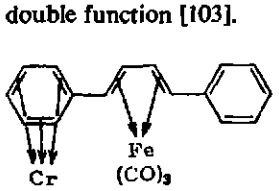


(21)

The spectrum of $C_4H_6Fe(CO)_3$ agrees with this molecular form. The position of the three equally intense proton signals in the NMR spectrum, at $\tau = 4.72$, 8.32, and 9.78, must be emphasized [31, 94]. These very distinctive chemical shifts of the protons, which are all bound to similarly hybridized carbon atoms, is explainable only by their different distances from the metal; the protons closest to the metal are screened to the greatest extent, and, as a result, their resonance lines are displaced into the "aliphatic region".

Analogous relations are encountered in other butadiene complexes, such as $(C_4H_6)_2Mo(CO)_2$ [121], $[C_4H_6Co(CO)_2]_2$ [111], $C_4H_6VC_5H_5(CO)_2$ [121], or $C_4H_6MnC_5H_5(CO)$ [121], as well as in the corresponding isoprene and 2,3-dimethylbutadiene compounds. The NMR spectra of $C_4H_4(CH_3)_2Fe(CO)_3$ and $C_4H_5CH_3Fe(CO)_3$ have recently been evaluated for the first time from the chemical shifts and the coupling constants. Good agreement was obtained with the observed values [148]. Starting from a comparison of the coupling constants for free and complexed isoprene (in $C_4H_5CH_3Fe(CO)_3$), it can be deduced that the π-electrons in $C_4H_5CH_3Fe(CO)_3$, just like those in $C_4H_6Fe(CO)_3$, are completely delocalized [148].

An interesting type of compound is obtained from 1,4-diphenylbutadiene. This substance reacts with iron carbonyls as a diene, yielding yellow-orange crystals of $C_4H_4(C_6H_5)_2Fe(CO)_3$ [103, 104]. In contrast, 1,4-diphenylbutadiene functions as a benzene derivative in the reaction with $Cr(CO)_6$, so that substituted aromatic-chromium tricarbonyls of composition $C_4H_4(C_6H_5)_2CrCO_3$ or $C_4H_4(C_6H_5)_2[Cr(CO)_3]_2$ are formed. The butadiene grouping is evidently still present in these compounds, since on further reaction with $Fe(CO)_5$ or $Fe_3(CO)_{12}$, they afford mixed 1,4-diphenylbutadiene-chromium carbonyl-iron carbonyl complexes of structure *(22)* or *(23)* [103, 104]. Here the $C_4H_4(C_6H_5)_2$ acts both as an olefinic and as an aromatic system. Other substituted diolefins probably can also exercise such a double function [103].



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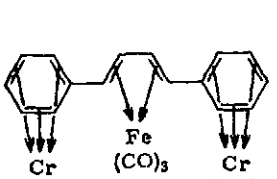
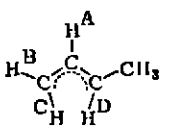


(23)

Butadieneiron carbonyls are also known in which the diene serves only as a monofunctional ligand. The $C_4H_6Fe(CO)_4$ synthetized recently [187] corresponds to the cation $[C_5H_5Fe(CO)_2C_4H_6]^+$ [129], which is prepared from $C_5H_5Fe(CO)_2Br$, C_4H_6, and a halogen acceptor such as $ZnCl_2$. This cation can be precipitated from its aqueous solution as the hexafluorophosphate and shows an infrared absorption at 1626 cm^{-1}. $C_4H_6Fe(CO)_4$ is formed, together with orange-yellow, crystalline $C_4H_6Fe_2(CO)_8$, as a distillable liquid that is extremely sensitive to air and light by passing butadiene into a suspension of $Fe_2(CO)_9$ in hexane (yield: *ca.* 60 %). An intense peak in the infrared spectrum at 1620 cm^{-1} corresponds here to the double bond not used in complex formation.

The action of butadiene on metal carbonyls also provides a means of preparing π-methallyl complexes. A compound "$C_8H_7O_4Co$" [179] obtained in 1952 from $HCo(CO)_4$ and C_4H_6 was later shown to be $C_7H_7O_3Co$ [180]. On the basis of its NMR spectrum [181], it is formulated as π-methallylcobalt tricarbonyl $C_4H_7Co(CO)_3$. The C_4H_7 residue, like the C_5H_5 residue, can be considered formally as a bifunctional ligand, since its π-electron system is delocalized. Since the CH_3 group can exist in *cis*-as well as in *trans*-relationship to the middle proton H_A *(24a* and *24b)*, two isomers are to be expected in all π-C_4H_7-metal compounds. This has been shown to be the case for $C_4H_7Co(CO)_3$ [181].



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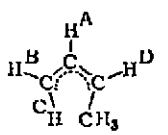

(24b)

The formation of $C_4H_7Co(CO)_3$ from $HCo(CO)_4$ and C_4H_6 may be explained as the addition of a hydrogen atom and the $[Co(CO)_4]$ residue onto the diene, probably in the *cis*-position, followed by elimination of CO from the σ-methallyl complex produced, thus leading to the π-methallyl complex [182]. In a manner similar to the reaction with $HCo(CO)_4$, reaction of $[C_5H_5Cr(CO)_3]_2$ and $HMn(CO)_5$ with butadiene yields π-$C_4H_7CrC_5H_5(CO)_2$ [121, 183] and π-$C_4H_7Mn(CO)_4$ [184], respectively. In the latter reaction, it has been possible to isolate the intermediate σ-$C_4H_7Mn(CO)_5$ as a yellow, easily distillable liquid. A compound with the π-methallyl structure is also, surprisingly, the "butadiene-palladium dichloride", obtained from $[(C_6H_5CN)_2PdCl_2]$ and C_4H_6; it is described by *Slade* and *Jonassen* [62] as a dimer, but by *Coates* [185] as a monomer. According to NMR measurements [186], however, it is not a diene complex, but rather a $[(\pi\text{-}C_4H_6Cl)PdCl]_2$, *i.e.* a substitution product of dimeric π-allylpalladium chloride.

Received, July 13th, 1962 and August 9th, 1962 [A 254/69 IE]

[179] *W. W. Prichard*, US.-Patent 2600671 (June 1952).

[180] *H. B. Jonassen, R. J. Stearns*, and *J. Kenttämaa*, J. Amer. chem. Soc. *80*, 2586 (1958).

[181] *D. W. Moore, H. B. Jonassen*, and *T. B. Joyner*, Chem. and Ind. *1960*, 1304.

[182] See *R. F. Heck* and *D. S. Breslow*, J. Amer. chem. Soc. *83*, 4023 (1961).

[183] *H. P. Fritz, H. Keller*, and *E. O. Fischer*, Naturwissenschaften *48*, 518 (1961).

[184] *W. R. McClellan, H. H. Hoehn, H. N. Cripps, E. L. Muetterties*, and *B. W. Howk*, J. Amer. chem. Soc. *83*, 1601 (1961).

[185] See [48], p. 339.

[186] *B. L. Shaw*, Chem. and Ind. *1962*, 1190.

[187] *H. D. Murdoch* and *E. Weiss*, Helv. chim. Acta *45*, 1156 (1962).

Preparation of a Diethylzinc-isoquinoline Coordination Complex

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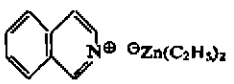
Politecnico di Milano (Italy)

Organometallic zinc compounds have little tendency to form electron-deficient complexes with Lewis bases [1, 2]. We have, however, succeeded in isolating a fairly stable 1:1 coordination complex



by using a strong base such as isoquinoline as electron donor. The complex is obtained as a viscous oil when diethyl zinc is added slowly to an excess of isoquinoline in an inert atmosphere, either with or without a hydrocarbon solvent. The reaction is exothermic.

The complex can be crystallized from n-pentane as small, bright yellow needles (m.p. 9–10 °C, uncorr.). The product cannot be distilled without decomposition; it dissociates into its components at 60 °C/0.2 mm. It is sensitive toward both air and moisture.

Cryoscopic determination of its molecular weight in benzene gave values of 258.1, 252.1, and 249 (theor. 252.65) at concentrations of 5.4, 3.3, and 2.4 %, respectively. The specific conductivity of the complex in toluene solution is of the order of 1×10^{-4} ohm^{-1} cm^{-1}; this excludes the possibility of an ionic structure. An infrared analysis, carried out to confirm the formation of the complex, shows that the bands characteristic of isoquinoline have been shifted in a manner typical for complexes of this type. On oxidation with dry air, the complex forms a deep red, highly viscous oil, which cannot be crystallized and which is currently being characterized.

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[1] *K. L. Thiele*, Angew. Chem. *71*, 650 (1959).

[2] *G. E. Coates:* Organometallic Compounds. Methuen, London 1960, p. 66.

Heterosiliconates with Organo-antimony Cation [1]

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We have prepared novel heterosiliconate anions by interaction of alkali organosiloxides with organosiloxy compounds of trivalent metals [2]. Their monomeric siloxane skeleton corresponds to the structural units of the polymeric feldspars. We have now succeeded in synthetizing salts in which such feldspar lattice fragments saturated with organic groups are associated with organometallic cations. Heptamethyl stibiosiloxane [3] reacts with equivalent amounts of tris-trimethylsiloxy-aluminum, -gallium, or -iron in CCl_4 solution even at room temperature, and well-formed crystals of tetramethylstibonium tetrakis-trimethylsiloxy-aluminate, -gallate, or -ferrate separate:

$$2\ Me_4SbOSiMe_3 + [(Me_3SiO)_3X]_2 \longrightarrow$$

(Me = CH_3; X = Al, Ga, or Fe). Table 1 presents the physical data of these compounds, which are stable in air and soluble in organic solvents. From these, the presence of complex, homopolar structures might be inferred.

Table 1. Stibonium heterosiliconates

	M.p. [°C]	Subl.temp. [°C/mm]	Color
$[Me_4Sb]^{\oplus}\,[Al(OSiMe_3)_4]^{\ominus}$ *(1)*	180.5	180 °/1	colorless
$[Me_4Sb]^{\oplus}\,[Ga(OSiMe_3)_4]^{\ominus}$ *(2)*	190.5	190 °/1	colorless
$[Me_4Sb]^{\oplus}\,[Fe(OSiMe_3)_4]^{\ominus}$ *(3)*	193	190 °/1	yellowish

Proton-NMR spectra and X-ray structural analyses prove, however, that the new heterosiliconates have purely ionic structures. Compounds *(1)* and *(2)* each show two sharp NMR signals (integral proportions 1:3); this proves unequivocally the equivalence of all four methyl groups attached to the antimony and of all four trimethyl siloxy groups on the aluminum and gallium, respectively [4]. Table 2 summarizes [5] the dimensions of the crystal unit cells and symmetry properties of the isomorphously orthorhombic compounds. A two-dimensional crystal analysis of *(1)* indicated that its structure consists of ideally tetrahedral tetramethylstibonium cations and tetrakis-trimethylsiloxy-aluminate anions of almost equal size. The bond lengths were calculated as Sb–C 2.20, Al–O 1.79, Si–O 1.56, and Si–C 1.88 Å. The angle Al–O–Si was 147°, all the others are almost exactly tetrahedral angles. The bond lengths and angles of the novel organosilico-aluminate anion thus correspond rather exactly to the dimensions of purely inorganic alkali aluminosilicates and of quartz [5].

Table 2. Unit cells and symmetry properties [5]

	a [Å]	b [Å]	c [Å]	U [Å^3]	$d_{meas.}$	$d_{calc.}$	Z	lattice group
(1)	13.41_2	11.88_4	9.89_9	1578	1.17	1.191	2	Pmmn
(2)	13.45_0	11.93_6	9.86_9	1584	1.26	1.275	2	Pmmn
(3)	13.50_8	11.95_3	9.81_6	1585	1.25	1.246	2	Pmmn

Received, November 12th, 1962 [Z 400/230 IE]

[1] Communication No. XI on Organometaloxanes. Communication No. X: *H. Schmidbaur* and *M. Schmidt*, Angew. Chem. internat. Edit. *1*, 549 (1962).

[2] *H. Schmidbaur* and *M. Schmidt*, Angew. Chem. internat. Edit. *1*, 328, 549 (1962); J. Amer. chem. Soc. *84*, 3600 (1962).

[3] *H. Schmidbaur* and *M. Schmidt*, Angew. Chem. *73*, 655 (1961).

[4] Varian A 60; concentration: 0.4 % in CS_2 and CCl_4, tetramethylsilane as internal standard. Compound *(3)* is paramagnetic.

[5] Thanks are due to Dr. *P. J. Wheatley*, Monsanto Research S. A., Zurich (Switzerland), for carrying out these investigations; to be published in detail in J. chem. Soc. (London).

Synthesis of 1-^{14}C-Labelled Polyunsaturated Fatty Acids

By Priv.-Doz. Dr. Dr. W. Stoffel and
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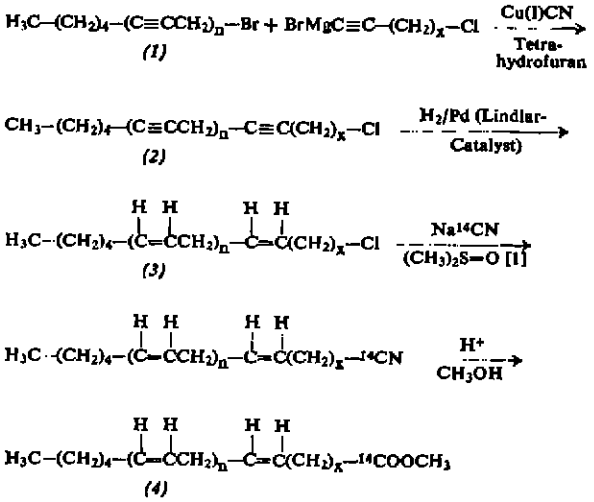
(Germany)

During the course of investigations on the mechanism of the biosynthesis of highly unsaturated fatty acids, we have devised a generally applicable method for the total synthesis of polyenoic acids containing a 1-^{14}C-labelled carboxyl group.

1-^{14}C-all-*cis*-Octadeca-9,12-dienoic acid (linoleic acid), 1-^{14}C-all-*cis*-octadeca-6,9,12-trienoic acid (γ-linolenic acid)

and 1-^{14}C-all-*cis*-eicosa-5,8,11,14-tetraenoic acid (arachidonic acid) were synthetized according to the following reaction scheme:



The nitrile synthesis with Na^{14}CN and the subsequent acid-catalysed hydrolysis of the nitrile each gave yields of over 90 %. The purity of the intermediates and of the methyl esters of the polyene acids (Table 1) was ascertained by gas chromatography, hydrogen number, ultraviolet and infrared spectroscopy, and isomerisation with alkali.

Table 1. Physical properties of the intermediates and of the methyl esters of polyenoic acids synthetized.

$H_3C-(CH_2)_4-(C\equiv CCH_2)_n-Br$ *(1)*

n = 1; b.p. 90–91 °C/12 mm; $n_D^{20} = 1.4862$
n = 2; b.p. 100–102 °C/0.1 mm; $n_D^{20} = 1.5115$
n = 3; b.p. 140 °C/0.1 mm; $n_D^{20} = 1.5252$

$HC\equiv C(CH_2)_x-Cl$

x = 7; b.p. 94–95 °C/13 mm; $n_D^{20} = 1.4549$
x = 4; b.p. 144 °C; $n_D^{20} = 1.4480$
x = 3; b.p. 116 °C; $n_D^{20} = 1.4448$

$H_3C-(CH_2)_4-(C\equiv CCH_2)_n-C\equiv C(CH_2)_x-Cl$ *(2)*

n = 1; x = 7; $n_D^{20} = 1.4804$ [*]
n = 2; x = 4; $n_D^{20} = 1.4985$ [*]
n = 3; x = 3; m.p. 18–20 °C; colorless needles.

[*] Purified by molecular distillation [2] at 80–130 °C (bath temperature)/10^{-4} mm.

$H_3C-(CH_2)_4-(C{=}CCH_2)_n-C{=}C(CH_2)_x-Cl$ *(3)*

n = 1; x = 7; $n_D^{20} = 1.4702$ [**]
n = 2; x = 4; $n_D^{20} = 1.4778$ [**]
n = 3; x = 3; $n_D^{20} = 1.4870$ [**]

[**] Purified by molecular distillation at 70–100 °C (bath temperature)/10^{-4} mm or by preparative gas chromatography.

$H_3C-(CH_2)_4-(C{=}CCH_2)_n-C{=}C(CH_2)_x-COOCH_3$ *(4)*

n = 1; x = 7; $n_D^{20} = 1.4620$; linoleic acid [+]
n = 2; x = 4; $n_D^{20} = 1.4672$; γ-linolenic acid [+]
n = 3; x = 3; $n_D^{20} = 1.4797$; arachidonic acid [+]

[+] Purified by molecular distillation at 100–130 °C (bath temperature)/10^{-4} mm or by preparative gas chromatography.

Received, October 11th, 1962 [Z 369/252 IE]

[1] *R. A. Smiley* and *C. Arnold*, J. org. Chemistry *25*, 257 (1960).
[2] *E. Klenk* and *H. Mohrhauer*, Hoppe-Seylers Z. physiol. Chem. *320*, 218 (1960).

Cycloheptatrieno-Indene

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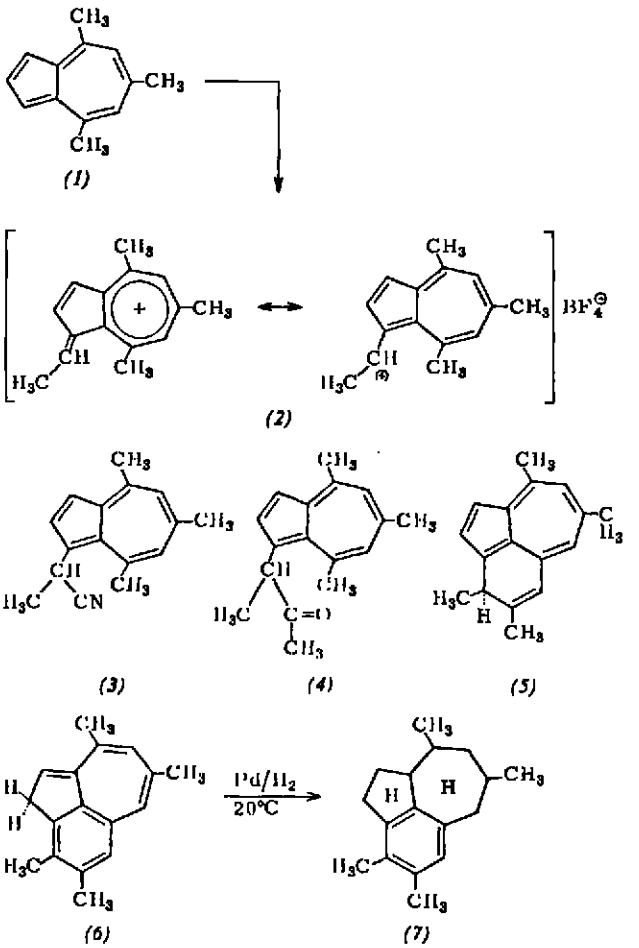
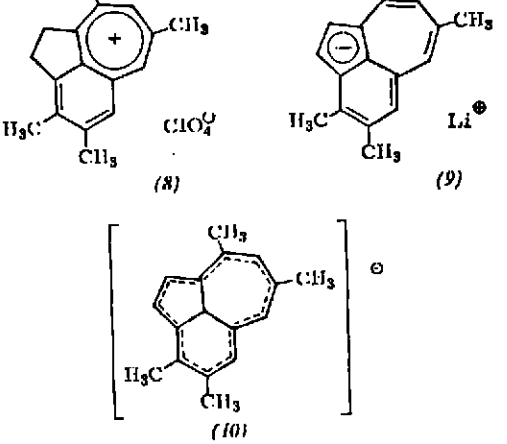
der Universität München (Germany)

Starting from 4,6,8-trimethylazulene *(1)* [1], we were able to prepare a non-benzenoid isomer of perinaphthalene, *viz.* cycloheptatrieno-indene or 2*H*-benz[*c*,*d*]azulene *(6)* [2]. Condensation of *(1)* with acetaldehyde in the presence of HBF_4 in ether affords *(2)* [3], which with sodium cyanide yields *(3)*, m.p. 111–112 °C.



This was converted with methylmagnesium bromide into the ketone *(4)*, m.p. 84–85 °C. With sodium *N*-methylaniline [4], *(4)* reacts immediately to give *(6)*. The intermediate *(5)*, which without doubt is formed first, changes with loss of the



azulenoid system resonance into the energetically more favorable benzenoid system *(6)*. Compound *(6)* crystallizes in golden-yellow needles of m.p. 116 to 117 °C; its ultraviolet spectrum has a strong fine structure: λ_{max} = 231 mμ (log ε = 4.55); 235 (4.55); 280 (3.91); 291 (3.80); 312 (3.71); 325 (3.69); 340 (3.59); and 406 (3.20).

Compound *(6)* absorbs 3 moles of H_2 to form the indane derivative *(7)*. With trityl perchlorate, *(6)* gives the stable orange carbonium salt *(8)*, m.p. 236 to 238 °C with decomposition. With methyl-lithium, *(6)* forms a green compound *(9)*, which is sensitive to hydrolysis. Compound *(9)* is an example of a cyclic conjugated 14 π-electron system with the general structure *(10)*.

Received, November 19th, 1962 [Z 392/242 IE]

[1] *K. Hafner* and *H. Kaiser*, Liebigs Ann. Chem. *618*, 140 (1958).

[2] *A. M. Patterson, L. T. Capell,* and *D. F. Walker:* The Ring Index. 2nd Edition, American Chemical Society, Washington, D.C., 1960, p. 409.

[3] *K. Hafner, H. Pelster,* and *J. Schneider*, Liebigs Ann. Chem. *650*, 62 (1961).

[4] *K. Hafner* et al., Liebigs Ann. Chem. *650*, 80 (1961); *624*, 37 (1959).

N-Ethoxycarbonylazepine

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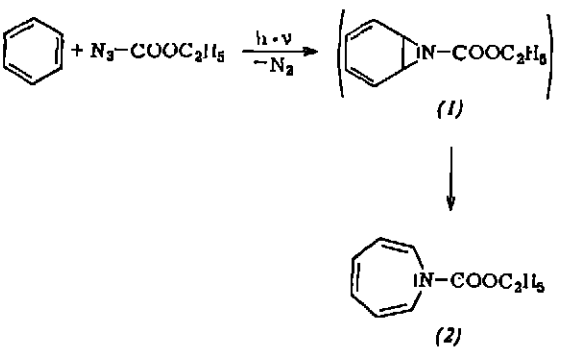
der Universität München (Germany)

By irradiating a solution of ethyl azidocarbonate in benzene with ultraviolet light, we obtained *N*-ethoxycarbonylazepine *(2)* in *ca.* 70 % yield as a stable yellow oil, b.p. 130 °C/20 mm (λ_{max} = 208 mμ (log ε = 4.44) and λ_{max} = 330 mμ (log ε = 2.72) in n-hexane).



This new ring expansion reaction resembles the photolytic reaction of benzene with diazomethane to yield cycloheptatriene. Here, however, instead of the methylene group, the ethoxycarbonylazene group [1] reacts with the benzene, probably to give first the azanorcaradiene derivative *(1)*, which rearranges at once to its isomeric azepine *(2)*.

Compound *(2)* is the first monocyclic azepine derivative to have been prepared [2]. Catalytic hydrogenation of *(2)* with Pd/H_2 at 20 °C affords *N*-ethoxycarbonyl hexamethylene imine (b.p. 118–120 °C/20 mm; n_{21}^D = 1.4635), which we also prepared from hexamethylene imine [3] and ethyl chloroformate. The two products proved to be identical, judging from their infrared and nuclear magnetic resonance spectra. The NMR-spectrum of *(2)* shows a multiplet for the 6 ring protons at 4–4.7 τ, in addition to the characteristic signals for the protons of the ethyl group (quartet at 5.8 τ, triplet at 8.7 τ).

The stability of the 8 π-electron system in *(2)* appears to be due at least in part to the claim on the free electron pair on the nitrogen made by mesomerism of the urethane system. In the presence of protic acids, *(2)* resinifies rapidly at 20 °C. Attempts to extend this ring expansion reaction with azides to other aromatic systems are in progress.

Received, November 20th, 1962 [Z 396/243 IE]

[1] *W. Lwowski* and *Th. W. Mattingly*, Tetrahedron Letters *1962*, 277.

[2] *K. Dimroth* and *H. Freyschlag*, Chem. Ber. *89*, 2602 (1956); *90*, 1628 (1957); *R. Huisgen* and *M. Appel, ibid. 91*, 12 (1958); *R. Huisgen* et al., *ibid. 93*, 392 (1960); Liebigs Ann. Chem. *630*, 128 (1960, *etc.*

[3] *L. Ruzicka* et al., Helv. chim. Acta *32*, 544 (1949).

Synthesis of Dehydroquinolizinium Systems

By Prof. Dr. O. Westphal and Dipl.-Chem. G. Feix

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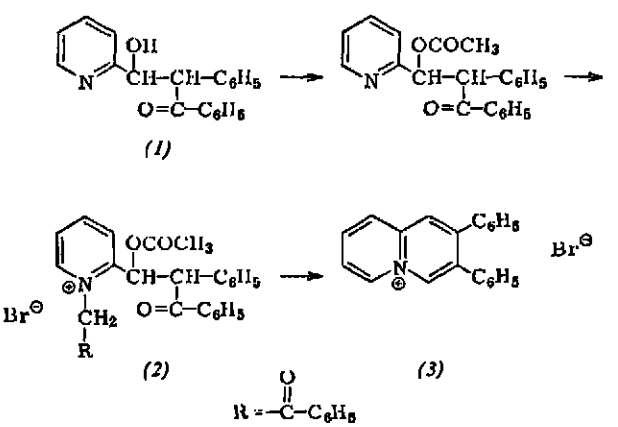
It has been shown [1] that 1,2-diketones can be condensed readily with *N*-methylene-α-picolinium salts to give dehydroquinolizinium derivatives. Here the first component supplies the two ketonic groups necessary for cyclization, and the second supplies the two activated methylene groups. We have now gone over to using two reactants, each of which contains both a ketonic group and an activated methylene group, so that monoketonic compounds derived from *N*-methylene-pyridinium-2-aldehyde can be used for the synthesis of dehydroquinolizinium systems.

The 1,3-ketol *(1)* formed from pyridine-2-aldehyde and deoxybenzoin was esterified and converted into the quaternary ammonium salt *(2)* using bromoacetophenone; the salt *(2)* was then cyclized using dibutylamine in boiling acetone to give 2,3-diphenyl-dehydroquinolizinium bromide *(3)*. In this way, as also in the synthesis mentioned above [1], the activating residue R is split off as benzoic acid. The yields of the individual reaction stages are between 65 and 80 %.



Judging from its melting point (284–285 °C), mixed melting-point, and infrared spectrum, compound *(3)* is identical with the compound obtained from benzil and *N*-carbethoxy-α-picolinium bromide [2].

Received, November 19th, 1962 [Z 398/222 IE]

[1] *O. Westphal, K. Jann,* and *W. Heffe*, Arch. Pharmac. *294*, 37 (1961).

[2] *K. Jann*, Ph. D. thesis, Universität Freiburg/Breisgau, 1958.

Bis-Silylated Carboxamides

By Prof. Dr. L. Birkofer, Dr. A. Ritter and Dipl.-Chem. W. Giessler [1]

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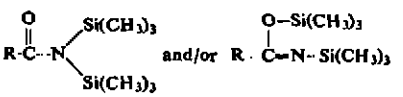
der Universität Köln (Germany)

Silylation of 1 mole of acetamide with 1 mole of trimethylchlorosilane in the presence of triethylamine gives *N*-trimethylsilylacetamide [2]. On the other hand, reaction of a

fairly large excess of trimethylchlorosilane with 1 mole of acetamide under the same conditions produced in good yield a carboxamide which is bis-silylated at the amide group, *viz.* the hitherto unknown bis(trimethylsilyl)acetamide *(1)*. This is a colorless liquid (b.p. 67.5 °C/30 mm) and is very sensitive towards hydrolysis. It proved possible in the same way to transform acrylamide into bis(trimethylsilyl)acrylamide *(2)*, a colorless liquid of b.p. 73.5 °C/22 mm. Investigations are in progress to decide between the two structures possible in each case.



(1) R = CH_3 *(2)* R = $H_2C=CH$

Limburg and *Post* [3] thought that they had prepared *(1)* by a reaction between ketene and hexamethyldisilazane, $[(H_3C)_3Si-NH-Si(CH_3)_3]$. The very high boiling point (61.5 °C/0.15 mm) differs from that of our product, and the analytical data do not correspond to the required values; this proves that these authors had not obtained the substance claimed.

Received, December 4th, 1962 [Z 405/229 IE]

[1] 17th Communication on organosilicon compounds; 16th Communication: *L. Birkofer, A. Ritter,* and *H. Dickopp,* Chem. Ber., in the press.

[2] *L. Birkofer, A. Ritter,* and *H. Dickopp,* Chem. Ber., in the press.

[3] *W. W. Limburg* and *H. W. Post,* Rec. Trav. chim. Pays-Bas *81*, 430 (1962).

Preparation, Properties and Crystal Structure of Potassium Hexafluorotechnetate(IV)

By Dr. K. Schwochau and Prof. Dr. W. Herr

Arbeitsgruppe „Institut für Radiochemie" der Kernforschungsanlage Jülich (Germany) and Institut für Kernchemie der Universität Köln (Germany) [*]

In analogy with the preparation of the corresponding rhenium compound [1], we obtained $K_2(^{99}TcF_6)$ on melting $K_2(TcBr_6)$ with KHF_2. Potassium fluorotechnetate was isolated in a pure state and in 60–70 % yield by recrystallization from water as pale pink, hexagonal platelets. The solubility of the salt at 25 °C was 1.5 g in 100 g of water.

The absorption spectra of the $(TcF_6)^{2-}$ and $(ReF_6)^{2-}$ ions are extensively similar in the visible, ultraviolet, and infrared regions, as was to be expected. While the other hexahalogen complexes of tetravalent technetium and rhenium do not absorb in the infrared spectral region of 4000–400 cm^{-1}, an intensive band was found for $K_2(TcF_6)$ at 574 cm^{-1} (17.4 μ), and one for $K_2(ReF_6)$ at 550 cm^{-1} (18.2 μ); these are to be assigned to the Tc–F and Re–F oscillations respectively.

The resistance of the fluorotechnetate to hydrolytic decomposition is particularly noteworthy. Chloro-, bromo-, and iodotechnetate (IV) all undergo hydrolysis even in weakly acid solution but $(TcF_6)^{2-}$ only in hot conc. aqueous alkali.

According to X-ray structural investigations, $K_2(TcF_6)$ crystallizes at room temperature in the trigonal $K_2(GeF_6)$ type [2] with lattice constants $a = 5.807 \pm 0.002$ Å and $c = 4.645 \pm 0.002$ Å, and is isomorphous with $K_2(ReF_6)$ [1, 3] and a modification of $K_2(MnF_6)$ [4] at low temperature. The density of potassium fluorotechnetate was measured as $\rho = 3.58 \pm 0.01$ g/cm³ [4]. It follows from this and from the crystal structure that the unit cell contains one formula element.

Miss *A. Sieburg* carried out the investigations on the rhenium compounds.

Received, December 5th, 1962 [Z 404/228 IE]

[*] At present situated in the Max-Planck-Institut für Chemie (Otto-Hahn-Institut) in Mainz, Germany.

[1] *E. Weise,* Z. anorg. allg. Chem. *283*, 377 (1956).

[2] *J. L. Hoard* and *W. B. Vincent,* J. Amer. chem. Soc. *61*, 2849 (1939).

[3] *R. D. Peacock,* Chem. and Ind. *1955*, 1453.

[4] *H. Bode* and *W. Wendt,* Z. anorg. allg. Chem. *269*, 165 (1952).

[5] Density determination: cf. *K. Schwochau,* Z. Naturforsch. *17a* 630 (1962).

Complexes of Molybdenum(III) with 1,3-Diketones

By Dipl.-Chem. K. Christ and Prof. Dr. H. L. Schläfer

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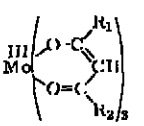
We have prepared the following co-ordination compounds of trivalent molybdenum:



where	R^1	R^2
	CH_3	CH_3
	CH_3	CF_3
	C_6H_5	CH_3
	C_6H_5	C_6H_5
	CF_3	C_4H_3S

The following diketones were used: *(1)* acetylacetone [1], *(2)* trifluoroacetylacetone, *(3)* benzoylacetone, *(4)* dibenzoylmethane, and *(5)* thenoyltrifluoroacetone.

The ketones *(1)* and *(2)* were treated with $K_3[Mo^{III}Cl_6]$ in aqueous methanol at room temperature, the acid formed being buffered with ammonium acetate. The compounds precipitate after fairly prolonged standing. Molybdenum(III)-tris-acetylacetonate was recrystallized from a mixture of n-hexane and tetrahydrofuran (2:1), while n-hexane was used for molybdenum(III)-tris-trifluoroacetylacetonate.

Solubility difficulties arise with ketones *(3)*, *(4)*, and *(5)* but can be circumvented by using a ternary mixture of dioxan/methanol/water as reaction medium and $(NH_4)_2[Mo^{III}Cl_5(H_2O)]$ as starting material. The required compounds were then obtained by fairly prolonged and vigorous stirring at room temperature followed by evaporation of the solvent *in vacuo*. The products are deep red-brown to black. They dissolve in organic solvents such as benzene, tetrahydrofuran, CCl_4, and partially in n-hexane to give deep red-black solutions. Several of the compounds become hot spontaneously in air. As the size of the organic ligand increases, the tendency to give tarry products during this process grows. All manipulations must be carried out under highly purified nitrogen, and it is essential to remove carefully any traces of dissolved oxygen from the solvents.

The preparation of the compounds mentioned and the results of investigations of their optical and magnetic properties will be published in the near future.

Received, December 7th, 1962 [Z 410/236 IE]

[1] Molybdenum(III)-trisacetylacetonate has also been prepared by *M. L. Larson* and *F. W. Moore,* J. inorg. Chem. *1*, 856 (1962).

Barium Halogenonitrides

By Prof. Dr. P. Ehrlich, Dr. E. Koch and Dipl.-Chem. V. Ullrich

Institut für Anorganische und Analytische Chemie der Universität Gießen (Germany)

Continuing an earlier investigation [1] of the chloronitrides of alkaline earth metals, in which the existence of the compounds Ca_2NCl and Ba_2NCl was verified, the systems

$Ba_3N_2/BaBr_2$ and Ba_3N_2/BaI_2 were examined. On fusing $BaBr_2$ and Ba metal in a molar ratio of 1:3 in the presence of nitrogen, a black lustrous product was obtained, which was identified as a hitherto unknown compound, Ba_2NBr. It is distinguished by a melting point maximum at 920 °C in the phase diagram of the system $Ba_3N_2/BaBr_2$. The two eutectics are at 19 mole-% Ba_3N_2 and 610 °C and at 87 mole-% Ba_3N_2 and 828 °C.

In the phase diagram of the Ba_3N_2/BaI_2 system, there is only one melting point maximum, *viz.* at 10 mole-% Ba_3N_2 and 810 °C, with accompanying eutectics at 2 mole-% Ba_3N_2 and 692 °C and at 20 mole-% Ba_3N_2 and 660 °C. A product with 10 mole-% Ba_3N_2 crystallizes as pale yellow, matted, fine needles and displays characteristic X-ray interference patterns which indicate a compound of formula Ba_6NI_9. The compounds Ba_2NBr and Ba_6NI_9 disintegrate readily on exposure to the atmosphere.

Received, December 7th, 1962 [Z 407/238 IE]

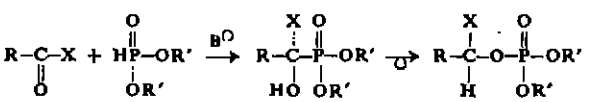
[1] *P. Ehrlich* and *W. Deissmann*, Angew. Chem. *70*, 656 (1958).

Synthesis of Aromatic or Heterocyclic Substituted Alkenes from Ketones

By Dr. U. Hasserodt and Prof. Dr. F. Korte

Shell Grundlagenforschung-GmbH.,
Schloß Birlinghoven (Germany)

The base-catalysed addition of dialkyl phosphites onto ketones generally yields dialkyl α-hydroxyphosphonates *(1)* [1]. In certain cases, however (X = CCl_3, $P(O)(OR')_2$, CN, or $CO-CH_3$) [2], phosphates *(2)*, produced by a rearrangement, or their secondary products, (X = CCl_3), *viz.* enolphosphates, were isolated.



(1) *(2)*

We have now found that the α-hydroxyphosphonate → phosphate rearrangement also takes place in presence of catalytic quantities of base when X is an aromatic group. However, the phosphates are difficult to isolate when R contains C–H bonds in the α-position to the C=O group; they are then extremely unstable and decompose slowly at room temperature or rapidly on distillation under reduced pressure, in both cases liberating considerable quantities of dialkyl phosphate and the corresponding olefin. The olefins may be isolated by the following procedure:

Equimolar quantities of *p*-chloroacetophenone and diethyl phosphite are treated with 3–10 mole-% of $NaNH_2$, keeping the temperature below 50 °C. The contents of the flask solidify, forming the α-hydroxyphosphonate *(1)*, m.p. 113 °C, and are then maintained at 140 °C for 90 minutes. During this time, the pH falls to about 3. After dissolving in water, several extractions with cyclohexane are performed, and pure *p*-chlorostyrene as verified by gas chromatography is obtained in 60% yield by distillation of the organic phase.

In the same manner, styrene was prepared from acetophenone (71%), *p*-bromostyrene from *p*-bromoacetophenone (60%), 2-vinylthiophene from 2-acetylthiophene (56%), and stilbene from benzyl phenyl ketone (81%).

Received, December 11th, 1962 [Z 408/241 IE]

[1] *V. S. Abramov*, Zhur. Obshchei Khim. *22*, 647 (1952), Chem. Abstr. *47*, 5351 (1953).

[2] *W. Lorenz, A. Henglein*, and *G. Schrader*, J. Amer. chem. Soc. *77*, 2554 (1955); *S. J. Fitch* and *K. Moedritzer*, ibid. *84*, 1876 (1962); *L. A. R. Hall, C. E. Stephens* and *J. J. Drysdale*, ibid. *79*, 1768 (1957); *V. A. Kuklitin, V. S. Abramov* and *K. M. Orekhova*, Proc. Acad. Sci. USSR. *128*, 903 (1959).

Alkyl- and Aryl-aminosulfanes Containing N-Silyl Groups

By Dr. O. Scherer and Prof. Dr. Max Schmidt

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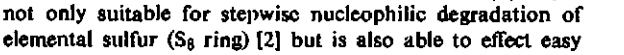
der Universität Marburg/Lahn (Germany)

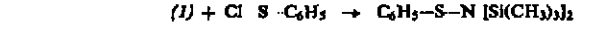
Sodium bis(trimethylsilyl)amide $[(CH_3)_3Si]_2NNa$ *(1)* [1] is not only suitable for stepwise nucleophilic degradation of elemental sulfur (S_8 ring) [2] but is also able to effect easy splitting of S–S bonds in sulfane derivatives, as we have done using alkyl- and aryl-disulfans. According to the equation:



the following unsymmetrical monosulfanes were formed almost quantitatively in benzene solution:

Phenyl-bis(trimethylsilyl)aminosulfane*(2)*, b.p. 87–88 °C/1 mm,
n-Butyl-bis(trimethylsilyl)aminosulfane, b.p. 71–72 °C/1 mm,
Ethyl-bis(trimethylsilyl)aminosulfane, b.p. 36–37 °C/1 mm.
The reactivity decreases in the order $C_6H_5 > C_2H_5 > C_4H_9$.

We also obtained *(2)* by the reaction



However, because of the disagreeable properties and generally very complicated preparation of chloro-organosulfanes ("sulphenyl chlorides"), nucleophilic scission of disulfanes according to equation (a) is a much better synthetic route leading to organo-aminosulfanes. A corresponding scission of long-chain organic sulfanes is currently under examination.

Received, December 12th, 1962 [Z 409/237 IE]

[1] *U. Wannagat* and *H. Niederpruem*, Chem. Ber. *94*, 1540 (1961).
[2] *O. Scherer* and *M. Schmidt*, Naturwissenschaften, in the press.

Acetylene Derivatives from a Fragmentation Reaction

By Prof. Dr. K. Bodendorf and Dr. P. Kloss

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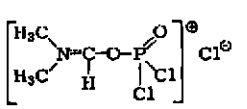
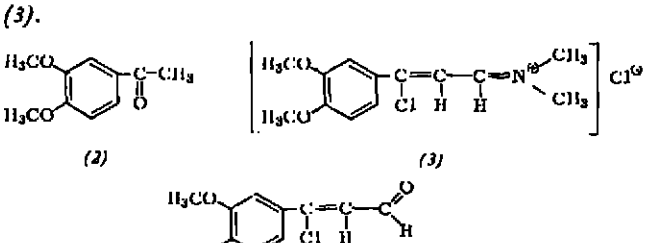
der Technischen Hochschule Karlsruhe (Germany)

The reaction of ketones with the Vilsmeyer-complex *(1)* gives α,β-unsaturated chloroaldehydes [1].



(1)

By treating acetoveratrone *(2)* with *(1)*, we were able to obtain β-chloro-3,4-dimethoxycinnamaldehyde *(4)* (m.p. 116–117 °C) in 60% yield, by hydrolysis of the intermediate *(3)*.



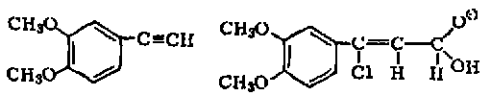
(2) *(3)*

(4)

With alkali, *(4)* gives 3,4-dimethoxyphenylacetylene *(5)* (m.p. 72–73 °C) [2] in approximately 80% yield.

In this reaction, the unstable intermediate *(6)* obviously arises by addition of a hydroxyl ion onto the aldehyde and

then decomposes into the acetylene derivative, chloride ion, and formic acid. In an analogous manner, we obtained phenylacetylene from acetophenone *via* chlorocinnamaldehyde



(5) (6)

and *p*-methoxyphenylacetylene from *p*-methoxyacetophenone *via* β-chloro-*p*-methoxycinnamaldehyde.

The new reaction makes it possible to prepare many acetylene derivatives relatively easily.

Received, December 14th, 1962 [Z 411/240 IE]

[1] *Z. Arnold* and *J. Zemlička*, Proc. chem. Soc. (London) *1958*, 227.

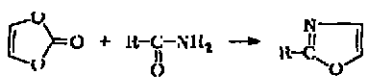
[2] *C. Schöpf* et al., Liebigs Ann. Chem. *544*, 61 (1940).

A New Synthesis of Oxazole

By Dr. P. G. Ferrini and Priv.-Doz. Dr. A. Marxer

Pharmazeutische Abteilung,
Forschungslaboratorien der CIBA AG., Basel (Switzerland)

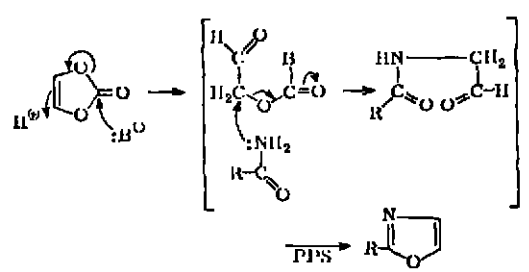
We have found that primary carboxamides may be condensed with vinylene carbonate *(1)* [1] in polyphosphoric acid to yield 2-substituted oxazoles *(2)*.



(1) (2)

Thus, condensation of equimolar quantities of benzamide and vinylene carbonate in polyphosphoric acid (2 hrs. at 165–170 °C) gave 2-phenyloxazole (b.p. 100–101 °/12 mm.) in 34% yield [2]. The corresponding reaction with *m*-nitrobenzamide gave 3-nitrophenyl-2'-oxazole (m.p. 99–99.5 °C) in 10% yield, and that with *o*-chlorobenzamide afforded 2-chlorophenyl-2'-oxazole (b.p. 100–105 °C/0.6 mm) in 6% yield. The reaction failed, however, when the following amides were employed: phenoxyacetamide, phenylacetamide, *p*-methylbenzamide, and salicylamide. Picolinic amide gave 2-(2'-pyridyl)oxazole in about 2% yield.

The formation of the oxazole may be accounted for by the following mechanism:



The consistently moderate yields could not so far be significantly improved when the reaction conditions were changed. Because of its simplicity, however, the present new synthesis appears to deserve further investigation.

Received, December 14th, 1962 [Z 413/239 IE]

[1] *R. W. Addor*, Ph. D. thesis (No. 1485), Ohio State University (1954); *M. S. Newman* and *R. W. Addor*, J. Amer. chem. Soc. *77*, 3789 (1955). We thank Dr. *H. Orth* of the CIBA AG., Basel, for a specimen of this compound.

[2] *J. W. Cornforth, R. H. Cornforth, E. P. Abraham, W. Baker, E. Chain*, and *R. Robinson:* The Chemistry of Penicillin. Princeton University Press Princeton, N.J., 1949, p. 704, as well as *W. E. Cass*, J. Amer. chem. Soc. *64*, 785 (1942) give a b.p. of 223–225 °C for 2-phenyl oxazole.

Reactions of Sulfur, Selenium, and Tellurium with Lithium Triphenylstannane

By Dr. H. Schumann, Dipl.-Chem. K. F. Thom and Prof. Dr. Max Schmidt

Institut für Anorganische Chemie
der Universität Marburg/Lahn (Germany)

Lithium triphenylstannane $Li \cdot Sn(C_6H_5)_3$ [1] was prepared readily from triphenylchlorostannane and lithium in tetrahydrofuran. It is an efficient nucleophilic reagent and undergoes stepwise reactions with sulfur, selenium, and tellurium in tetrahydrofuran at room temperature.

$$n\,(C_6H_5)_3SnLi + X_n \rightarrow n\,(C_6H_5)_3Sn{-}X{-}Li \qquad (X = S, Se, Te)$$
(1)

The pure monochalkogenide *(2)* is difficult to isolate and is formed only in the presence of a large excess of *(1)* (stoichiometric quantities of reactants yield a mixture of $(C_6H_5)_3S_nX_nLi$ products).

Solutions of *(2)* are very reactive and are sensitive toward air and heat (condensation to Li_2S and thioether if X = S). With triphenylchlorostannane, good yields of hexaphenylditin sulfide, hexaphenylditin selenide, and hexaphenylditin telluride (m.p. 148 °C) are obtainable. With benzoyl chloride, the sulfur compound readily forms triphenyltin thiobenzoate $(C_6H_5)_3Sn{-}S{-}CO{-}C_6H_5$ (m.p. 108 °C).

By reaction between *(2)* and triphenylbromogermanium or triphenylchlorolead:

$$(C_6H_5)_3SnXLi + BrGe(C_6H_5)_3 \rightarrow LiBr + (C_6H_5)_3SnXGe(C_6H_5)_3$$

such compounds as $(C_6H_5)_3SnSGe(C_6H_5)_3$ (m.p. 135 °C), $(C_6H_5)_3SnSeGe(C_6H_5)_3$ (m.p. 133 °C), and $(C_6H_5)_3SnSPb(C_6H_5)_3$ (m.p. 138 °C) are obtained; the methyl analogues of these compounds were prepared earlier by a different method [2].

Received, December 17th, 1962 [Z 412/235 IE]

[1] *G. Wittig* et al., Liebigs Ann. Chem. *571*, 167 (1951).

[2] *I. Ruidisch* and *M. Schmidt*, Chem. Ber., in the press.

Formation of Monochloroheptane Isomers during the Chlorination of n-Heptane with Trichloromethanesulfonyl Chloride

By Dr. B. Fell and cand. chem. Li-Hoan Kung

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If elemental chlorine is used for chlorinating n-alkanes of both low and fairly high molecular weights, the relative reactivities of primarily and secondarily bonded hydrogen atoms are found to be approximately in a ratio of 1:3 [1]. When the chlorination is brought about with chlorinating agents, such as *N*-chlorosuccinimide, t.-butyl hypochlorite, or trichloromethanesulfonyl chloride, secondary alkyl chlorides are formed preferentially beyond the 1:3 ratio, or even as practically the sole products.

We investigated the composition of a mixture of monochloroheptane isomers obtained by chlorinating n-heptane with trichloromethanesulfonyl chloride using peroxide to initiate the reaction. This mixture was compared with the composition of the reaction product obtained under otherwise equal conditions by chlorinating with elemental chlorine using initiation by ultraviolet light (see Table 1).

The surprising fact emerges that, in the chlorination with trichloromethanesulfonyl chloride, substitution at the first methylene group is clearly preferred. On the other hand, statistical substitution occurs as before at the carbon atoms further along the chain. Additional halogenation experiments

with *N*-chlorosuccinimide, t-butyl hypochlorite, *N*-bromosuccinimide, and other reagents are in progress in order to confirm these findings.

Table 1. Chlorination of n-heptane at 98 °C with trichloromethanesulfonyl chloride or elemental chlorine

Chlorinating agent	Hours	Catalyst	Composition of the monochloro-n-heptane fraction [% by wt.]			
			1-chloro-	2-chloro-	3-chloro-	4-chloro-
Cl_2 [a]	2	hν	15.1	34.6	33.8	16.5
CCl_3SO_2Cl [b]	5	C_6H_5COOOH (5 mole-%)	2.3	50.4	32.1	15.2
CCl_3SO_2Cl [c]	8	C_6H_5COOOH (5 mole-%)	1.9	50.3	32.0	15.8

[a] 14.2 g (0.2 mole) of Cl_2 were passed into 100.2 g (1 mole) of n-C_7H_{16} over 2 hours; monochloroheptane fraction: 19.9 g.
[b] 100.2 g (1 mole) of n-C_7H_{16} and 30.5 g (0.14 mole) of CCl_3SO_2Cl; monochloroheptane fraction: 12.8 g.
[c] 100.2 g (1 mole) of n-C_7H_{16} and 43.6 g (0.2 mole) of CCl_3SO_2Cl; monochloroheptane fraction: 20.0 g.

The reaction product was characterized by adsorption chromatography substantially according to *Asinger* et al. [2]. The isomer composition of the monochloride fraction was examined by gas chromatography. The separation and quantitative estimation of the isomeric n-heptyl chlorides was carried out using a column 16 m long containing 8 % β,β'-iminodipropionitrile on 60–80 mesh chromosorb R as stationary phase (80 °C, He as carrier gas). The gas chromatography equipment was a model 600 instrument made by Research Specialties Co., Richmond, Calif.

We thank Dr. *Elisabeth Bendel* for the gas chromatographic investigations.

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[1] Cf. *F. Asinger:* Chemie und Technologie der Paraffinkohlenwasserstoffe. Akademie-Verlag, Berlin 1956, p. 608 *et seq.*

[2] *F. Asinger, G. Geiseler,* and *K. Schmiedel,* Chem. Ber. *92,* 3085 (1959).

Additions of Organotin Hydrides onto Aldehydes, Ketones, and Azomethines

By Priv.-Doz. Dr. W. P. Neumann
and cand. chem. E. Heymann

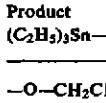
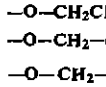
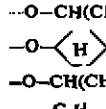
Chemisches Institut der Universität Gießen (Germany)

Addition of organotin hydrides onto carbonyl compounds or azomethines leads to organic compounds containing the Sn–O– and Sn–N– group, respectively [1]. It has now been shown that this new synthesis can be used in many ways and that, besides radical-forming compounds, $ZnCl_2$ is also a suitable catalyst. Hydrogenation of the unsaturated groups by the organotin hydrides, which takes place exclusively in the absence of catalysts [2], is largely suppressed.

$$R_3SnH + O{=}CR'R'' \rightarrow R_3Sn{-}O{-}CHR'R'' \quad (R' \text{ can also be H})$$
$$R_3SnH + R'{\cdot}\,CH{=}N\,R'' \rightarrow R'{-}CH_2{-}N(SnR_3)R''$$

The compounds in Table 1, and many others prepared by us, are easily hydrolysed. In moist air, gradual formation of the corresponding alcohol or secondary amine and of triethyl-tin carbonate $(R_3Sn)_2CO_3$ (decomposes at 137–140 °C with evolution of CO_2) occurs. Three additions of tributyltin hydride onto ketones under the influence of ultraviolet irradiation have recently been reported by *R. Calas* et al. [3].

Table 1. Products obtained from aldehydes, ketones, or azomethines and triethyltin hydride between 40 and 90 °C (in the absence of air)

Product $(C_2H_5)_3Sn{-}X$, X=	Obtained from	b.p. [°C/mm Hg]	Yield [c] of pure compound [%]
$-O-CH_2CH(CH_3)_2$	isobutyraldehyde [a]	95–96/11	80
$-O-CH_2-C_6H_5$	benzaldehyde [a]	150–155/14	[d]
	furfural [a]	121–125/12	[d]
$-O-CH_2-C_6H_4-OCH_3$	anisaldehyde [a]	132/0.04	75
$-O-CH(CH_3)C_2H_5$	methyl ethyl ketone [b]	93–96/12	95
	cyclohexanone [b]	69/0.1	61
$-O-CH(CH_3)-C_6H_4-OCH_3$	*p*-methoxyacatophenone[b]	90–93/10^{-4}	70
	benzal-*p*-toluidine [a, b]	142/10^{-3}	63

[a] Azoisobutyric dinitrile as catalyst [b] $ZnCl_2$ as catalyst.
[c] Mostly small-scale experiments. [d] Not determined.

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[1] *W. P. Neumann, H. Niermann,* and *R. Sommer,* Angew. Chem. *73,* 768 (1961).

[2] *J. G. Noltes* and *G. J. M. van der Kerk,* Chem. and Ind. *1959,* 294; *H. G. Kuivila* and *O. F. Beumel, jr.,* J. Amer. chem. Soc. *83,* 1246 (1961); *J. Valade, M. Pereyre,* and *R. Calas,* C. R. hebd. Séances Acad. Sci. *253,* 1216 (1961).

[3] *R. Calas, J. Valade* and *J. C. Pommier,* C. R. hebd. Séances Acad. Sci. *255,* 1450 (1962).

Expansion of Six-Membered Rings in Cyclopentadienyl-Benzene-Metal π-Complexes by Acylation

By Prof. Dr. E. O. Fischer and Dipl.-Chem. S. Breitschaft

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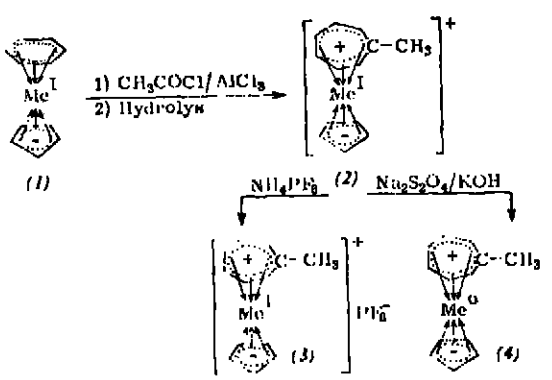
During experiments on the acylation of $C_5H_5CrC_6H_6$ [1] and $C_5H_5MnC_6H_6$ [2] using $AlCl_3$ according to Friedel-Crafts, we surprisingly obtained under mild conditions an approximately 10 % yield of cyclopentadienyl-metal π-complexes containing a substituted seven-membered ring as the second complexed ligand instead of a substituted benzene. Thus, acetylation in CS_2 and subsequent hydrolysis led to stable cations of empirical formulae $[C_{13}H_{14}Cr]^+$ and $[C_{13}H_{14}Mn]^+$, which could be precipitated as their hexafluorophosphates. These no longer contain the oxygen of the acid halide. The carbon atom which originally bore the oxygen is inserted into the six-membered ring, expanding it to form a seven-membered ring, while the methyl group bound to it becomes a substituent of the seven-membered ring.



(1), (2), (3) Me = Cr, Mn; (4) Me = Cr

Proof that the diamagnetic, pink, complexed Mn cation is the cyclopentadienyl(methylcycloheptatrienyl)manganese(I) cation $[C_5H_5MnC_7H_6{-}CH_3]^+$ is provided by the NMR-spectrum [3] of the hexafluorophosphate in acetone which contains three signals with τ-values of 5.53, 5.61, and 7.55 in the ratio of 6:5:3. The greenish yellow, paramagnetic $[C_{13}H_{14}Cr]^+$ cation (hexafluorophosphate, 2.1 Bohr mag-

netons, corresponding to one unpaired electron) has practically the same infrared spectrum as the Mn complex. The Cr cation can be reduced with alkaline $Na_2S_2O_4$ solution to give a neutral, diamagnetic, blue-black complex (m.p. 78 °C), for which an analogous structure, *viz.* cyclopentadienyl-(methylcycloheptatrienyl)chromium(O) $C_5H_5CrC_7H_6{-}CH_3$, can be deduced on the basis of its NMR spectrum [3] in C_6D_6, which has τ-values of 5.11, 6.83, and 8.00 in the ratio of 6:5:3.

This novel ring expansion also proceeds successfully with aromatic acid halides. In this way, we obtained the cations $[C_5H_5MnC_7H_6{-}C_6H_5]^+$ and $[C_5H_5CrC_7H_6{-}C_6H_5]^+$ from a reaction with $C_6H_5COCl/AlCl_3$ followed by hydrolysis; the second of these cations could again be reduced to a bright green, uncharged complex (m.p. 90–91 °C).

The structure of these new five- and seven-membered ring-metal compounds, which were for the first time produced by ring expansion of aryl-metal complexes, was confirmed with chromium by an independent synthesis. By using the method leading to $C_5H_5CrC_7H_7$ [4], we were able to introduce methyltropylidene and phenyltropylidene as substituted tropylium cations into $C_5H_5CrC_6H_6$ by displacement of the benzene and with attendant hydride elimination. During this process, $[C_5H_5CrC_7H_6{-}CH_3]^+$ und $[C_5H_5CrC_7H_6{-}C_6H_5]^+$ were formed in a smooth reaction in good yields and proved to be identical with the complexes prepared by ring expansion judging from their infrared spectra and, after reduction, from their NMR-spectra.

Received, December 19th, 1962 [Z 417/232 IE]

[1] *E. O. Fischer* and *H. P. Kögler*, Z. Naturforsch. *13b*, 197 (1958).

[2] *S. Breitschaft*, Diploma thesis, Universität München, 1962.

[3] Investigations by *H. P. Fritz*.

[4] *E. O. Fischer* and *S. Breitschaft*, Angew. Chem. internat. Edit., in the press.

Transnitrosation: a New Route to Oximes

By Dr. Carl Heinz Schmidt

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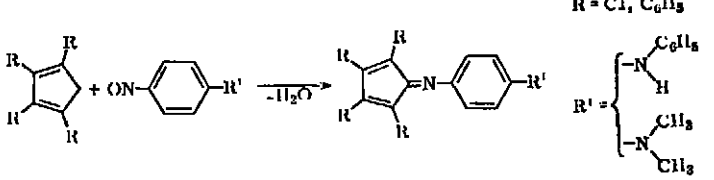
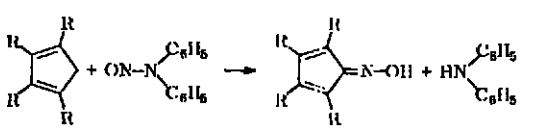
When aromatic *C*-nitroso compounds and cyclopentadienes react together, intensely colored 1-azafulvenes are formed *e.g.*:



On the other hand, surprisingly, aromatic *N*-nitroso compounds react with the reactive methylene group of 1,2,3,4-tetrachlorocyclopentadiene to form the oxime of the latter and secondary amines, *e.g.*:



The reaction proceeds without a catalyst on heating the reactants together in a polar solvent such as lower alcohols or glacial acetic acid, giving high yields. On passing from the purely aromatic diphenylnitrosamine to the aryl-aliphatic compound phenylmethylnitrosamine, we find that this reacts more slowly, while the purely aliphatic derivative dimethylnitrosamine does not react at all under these conditions.

Other compounds with active CH_2-groups are also suitable, *e.g.* pyrazolones, rhodanines, malonic dinitrile, and barbituric acids. *N*-Nitrosamides and the majority of cyclic and straight-chain saturated and unsaturated mono-, di-, and trinitrosamines do not react under the conditions stated above. However, transnitrosation was accomplished by addition of catalytic quantities of hydrochloric acid, which also induced dimethylnitrosamine to react.

The N–N bond in diphenylnitrosamine is so weakened by the electron attraction of the phenyl rings on the one hand, and of the oxygen of the nitrosyl group on the other that it is more easily broken when the reactants come into contact than the N–N bond in the aryl-aliphatic *N*-nitrosamine, in which the electron accepting property of the benzene ring is partly negated by the alkyl group. The failure of transnitrosation to occur with entirely aliphatic *N*-nitrosamines without a catalyst may be attributed to the strengthening of the N–N bond by electron donation from the alkyl groups.

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Phenol as Humification Inhibitor in Protein Hydrolyses

By Dr. F. Drawert and K.-H. Reuther

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During complete hydrolysis of animal and plant tissues with 6 N HCl for total amino acid analyses, considerable formation of dark insoluble precipitates often occurs (Maillard reaction; melanoidins, humic acids). In this way, considerable quantities of amino acids escape detection by the analysis. Various methods, not all of them satisfactory, have been described for avoiding these undesirable side reactions [1]. We have found that addition of phenol at the commencement of the hydrolysis is quite effective.

Thus, 4 ml of 80 % aqueous phenol are added to approximately 50 mg of dried and finely ground leaf material (vine leaves) in a thick-walled boiling tube and warmed to 50 to 60 °C for 5 min. After addition of 6 ml of 10 N HCl, the tube is sealed off and heated for 20 hrs at 105 °C. After cooling, the contents of the tube are transferred quantitatively to a separation funnel and extracted exhaustively with ether. The etheral solution of the phenol is then re-extracted with water. The combined aqueous phases are evaporated to dryness, and the residue is redissolved to prepare a standard solution for amino acid analysis.

Means of several analyses using an automatic amino acid analyser manufactured by Bender and Hobein, München (Germany)

Hydrolysis with	His	Lys	Arg	NH_3	Asp	Thr	Ser	Glu	Pro
6 N HCl	0.16	0.30	0.18	0.64	0.68	0.24	0.29	1.00	0.35
6 N HCl + phenol	0.20	0.60	0.52	4.20	1.80	0.88	0.81	2.30	0.62

Hydrolysis with	Gly	Ala	Val	Met	Ileu	Leu	Tyr	Phe	
6 N HCl	0.95	0.86	0.15	—	0.21	0.65	+	0.18	µmoles
6 N HCl + phenol	2.45	1.85	0.54	—	0.85	1.80	+	0.85	µmoles

Received, January 7th, 1963 [Z 428/254 IE]

[1] *E. Kofranyi*, Hoppe Seylers Z. physiol. Chem. *287*, 170 (1959); *J. P. Dustin*, *C. Czajkowska*, *S. Moore*, and *E. J. Bigwood*, Analytic. chim. Acta *8*, 236 (1953); *G. Krampitz*, Z. Tierphysiol. Tierernährg. u. Futtermittelkunde *15*, 227 (1960); *G. Schramm* and *J. Primosigh*, Hoppe-Seylers Z. physiol. Chem. *283*, 34 (1948).

Symposium on Plant Protection and Pesticides

Magdeburg (Germany), September 27th to 29th, 1962

From the Proceedings:

Synthesis of Chlorinated Propionic Acids with Herbicidal Activity

K. Smeykal and *H. Pallutz*, Leuna (Germany)

The synthesis of sodium α,α-dichloropropionate (Dalapon®, Omnidel Spezial®) and sodium α,α,β-trichloropropionate (TCP, Omnidel®) in the laboratory and on a pilot plant scale was described. The starting material for both salts is acrylonitrile. The synthesis of Na α,α-dichloropropionate is as follows:

$$H_2C{=}CH{-}CN \xrightarrow{\text{hydrogenation}} H_3C{-}CH_2{-}CN \xrightarrow{\text{chlorination}}$$

(1) *(2)*

$$H_3C{-}CCl_2{-}CN \xrightarrow{\text{hydrolysis}} H_3C{-}CCl_2{-}COOH \xrightarrow{\text{neutralisation}}$$

(3) *(4)*

$$H_3C{-}CCl_2{-}COONa + 2\,H_2O$$

(5)

Propionitrile *(2)* is produced by a continuous process involving partial hydrogenation of *(1)* at 140–150 °C and 240 atm. in the presence of sulfide catalysts, such as WS_2·NiS, and of diluents, which remain unchanged in the course of the reaction, *e.g.* alcohols (n-butanol, isobutanol, *etc.*) or propionitrile itself. α,α-Dichloropropionitrile *(3)* (b. p. 102 to 103 °C) is produced by treating propionitrile with chlorine at 45 °C. Hydrolysis of the chlorinated nitrile with 65% sulfuric acid at 125 °C gives *(4)* (b. p. 97–99 °C/20 mm Hg; m. p. 13–15 °C), which is treated with the equivalent amount of 50% sodium hydroxide at 50 °C to give the sodium salt *(5)*. Na α,α,β-trichloropropionate is prepared as follows:

$$H_2C{=}CH{-}CN \xrightarrow{\text{chlorination}} ClH_2C{-}CCl_2{-}CN \xrightarrow{\text{hydrolysis}}$$

$$ClH_2C{-}CCl_2{-}COOH \xrightarrow{\text{neutralisation}} ClH_2C{-}CCl_2{-}COONa + 2\,H_2O$$

Acrylonitrile is chlorinated at 50–60 °C in the presence of a trace of pyridine or pyridine homologues to give α,α,β-trichloropropionitrile (b. p. 64–66 °C/30 mm Hg). Hydrolysis to α,α,β-trichloropropionic acid (b. p. 112–114 °C/8 mm Hg; m. p. 61.5–62 °C) and neutralisation to give the sodium salt then follow in the same way as for Na α,α-dichloropropionate. The technical preparation of both herbicides is carried out in the same plant from the chlorination stage onward.

2-Styrylquinoline-N-oxide and its Biological Activity

G. Buchmann, Merseburg (Germany),
and *D. Kirstein*, Berlin (Germany)

Interest in substituted 2-styrylquinolines as tumoricidal compounds has been raised by *Bahner* and as dyes by *Voelting*. The amine oxides are prepared by:

1. Condensation of quinaldine with benzaldehyde, followed by *N*-oxidation and the introduction of substituents.

2. Condensation of substituted quinaldine-*N*-oxides.

The introduction of substituents into the molecule of 2-styrylquinoline is difficult, since on oxidation with 30% aqueous hydrogen peroxide in glacial acetic acid it is degraded to quinaldinic acid-*N*-oxide. Halogenation of 2-styrylquinoline gives dihalogenated compounds. Treatment of the dibromide of 2-styrylquinoline with alcoholic potash regenerates 2-styrylquinoline, but treatment with an alcoholic solution of sodium ethoxide gives the amine oxide.

Quinaldine-*N*-oxide and 4,7-disubstituted quinaldine-*N*-oxides condense only slightly or not at all with benzaldehyde in the presence of acid catalysts; however, introduction of an electron-acceptor group in the 4-position leads to good yields. Starting from 4-nitroquinaldine-*N*-oxide, many derivatives are obtainable. Ready substition of the nitro-group by chlorine or an alkoxy-group also takes place in the 2-styrylquinoline-*N*-oxides, so that derivatives substituted at C-4 can be prepared.

Investigations of the appropriate infrared spectra show that the substituents are in the *trans*-position with respect to the C=C double bond; any change from the *trans*- to the *cis*-form as a result of abnormal isomerization reactions in the 2-styrylquinoline molecule is detectable by infrared spectroscopy.

The 2-styrylquinoline-*N*-oxides show fungistatic and bacteriostatic activity.

Synthesis and Fungistatic Activity of Quinone Sulfide Derivatives

H. J. Dietz and *H. Grünzel*, Magdeburg (Germany)

The dependence of the fungistatic activity of *p*-benzoquinone and 1,4-naphthoquinone sulfide derivatives on the type, number, and position of the –S–R groups was systematically investigated. About 160 compounds containing alkylthio or arylthio groups were synthetized and tested. Their preparation was either by reaction of thiols with chlorinated quinones or by addition of thiols onto quinones. By stepwise addition, polysubstituted derivatives with the same or different –S–R groups were prepared. Cases of isomerism among the bis-(alkylthio)-*p*-benzoquinones were clarified. The main products from addition reactions were identical with those prepared by substitution of chlorine from 2,5-dichloro-*p*-benzoquinone. The isomeric bis-(alkylthio)-*p*-benzoquinones isolated in some cases as by-products gave the same 2,6-derivatives as those prepared directly from 2,6-dichloroquinones. Quinone sulfide derivatives containing chlorine were prepared either by direct chlorination or from thiols and chloroquinones. Finally, partial substitution of the chlorine in 2,3-dichloro-α-naphthoquinones by a single –S–R group was successfully effected by a special method. A series of quinone sulfides was converted further into Diels-Alder adducts and into oximes and semicarbazones.

The results of *in vitro* tests using a chromatographic method showed a relationship between chemical constitution and fungistatic activity. In a single series of compounds, activity declined with increasing size of the alkylthio group or increasing substitution of the arylthio residue. Comparisons from other points of view show other broad regularities. Optimum activity was shown by 2-alkylmercapto-3-chloro-α-naphthoquinones, which showed activity against numerous fungi equal to or greater than that of the standard fungicides (Phygon®, Captan®).

Systemic Fungicidal Activity of Pyridinecarboxyl Acid Derivatives

W. Harnack and *J. Schwarz*, Teltow-Seehof (Germany)

Of the three possible pyridinecarboxylic acids, isonicotinic acid and its derivatives in particular show systemic fungicidal activity. When celery plants were watered with *e.g.* isonicotinic hydrazide in concentrations of 0.5–0.05% and subsequently infected with *Septoria apii*, a delay in the onset of infection from 2 to 3 weeks compared with untreated

controls was observed. The same action was shown when application was effected both by spraying and via hydrocultures. No activity was shown against *Phytophthora infestans* on tomatoes. A similar but slightly weaker effect was exhibited by isonicotinic semicarbazide hydrochloride and by free isonicotinic acid and its ethyl ester.

Among the products of alkylation of the terminal *N*-atoms of isonicotinic hydrazide, a very slight increase in the inhibitory effect on infection was observed only in the case of isonicotinic ω-methylhydrazide hydrochloride. Quarternization of the ring nitrogen atom with alkyl halides of varying carbon-chain length invariably resulted in complete loss of systemic activity. Condensation of isonicotinic hydrazide with aldehydes such as salicylaldehyde and glyceraldehyde, and with glucose gave products of activity similar to that of the starting material. Of the condensation products with ketones, only the isonicotinoyl hydrazone of acetone had activity comparable to that of INH. The systemic activity observed on celery plants in the greenhouse could not be reproduced in field experiments. [VB 651/60 IE]

New Reactions of Metal Carbonyls and Cyano Complexes in Liquid Ammonia

H. Behrens, Erlangen (Germany)

Reactions with liquid NH_3 of mono- and polynuclear carbonyls of metals of the first long period proceed by the mechanisms:

a) Replacement of CO by NH_3 *e.g.* in $Cr(CO)_6$ [1] and $Ni(CO)_4$ [2];

b) Reduction to the carbonylometallate anion and oxidation of one CO molecule to $CO(NH_2)_2$ *e.g.* in $Fe(CO)_5$ [1,3], $Fe_2(CO)_9$ [3];

c) Disproportionation to a hexammine metal cation and a carbonylometallate anion; the liberated CO reacts further by b) *e.g.* with $Co_2(CO)_8$ and $Co_4(CO)_{12}$ [4].

Recent investigations have shown that disproportionations occur in the reactions of $Fe_3(CO)_{12}$ [3] and $Mn_2(CO)_{10}$ [4] with liquid NH_3. With the former, the following stages are known to occur:

i) $4\ Fe^0_3(CO)_{12} + 18\ NH_3 \rightarrow 3\ [Fe^{+II}(NH_3)_6]\ [Fe_3{}^{-II}(CO)_{11}] + 15\ CO$

ii) $[Fe(NH_3)_6]\ [Fe_3(CO)_{11}] + 2\ CO \rightarrow [Fe(NH_3)_6]\ [Fe_2(CO)_8] + Fe(CO)_5$

iii) $Fe^0(CO)_5 + 4\ NH_3 \rightarrow (NH_4)_2[Fe^{-II}(CO)_4] + CO(NH_2)_2$.

The reaction of $Mn_2(CO)_{10}$ in liquid NH_3, on the other hand, is characterized by the formation of a CO-containing cation $[Mn(CO)_3(NH_3)_3]^+$, which is isoelectronic with $Cr(CO)_3(NH_3)_3$, which is obtained from $Cr(CO)_6$ and liquid NH_3 at 120 °C:

$$Mn^0{}_2(CO)_{10} + 3\ NH_3 \rightarrow [Mn^{+I}(CO)_3(NH_3)_3]\ [Mn^{-I}(CO)_5] + 2\ CO.$$

Hexacarbonyls $M(CO)_6$ and their substitution compounds with 2,2'-dipyridyl of the type $M(CO)_4$ dipy, react with KCN in liquid NH_3 at temperatures above 60 °C, to form cyanocarbonylometallate(0) complexes of compositions $K_2[M(CO)_4(CN)_2]$ and $K_3[M(CO)_3(CN)_3]$, where M = Cr, Mo, or W [5].

With KCN in liquid NH_3, substitution products of $Ni(CO)_4$ of the type $Ni(CO)_2L_2$ yield the dicyanodicarbonylonickellate(0) complex $K_2[Ni(CO)_2(CN)_2]$; the reactions occur at the following temperatures:

L_2 =	dipy	o-phen	$2\ PF_3$
	−30 °C	−10 °C	30 °C

[Chemische Gesellschaft Erlangen (Germany), November 22nd, 1962] [VB 663/64 IE]

[1] *H. Behrens* et al., Angew. Chem. *74*, 120 (1962).

[2] *H. Behrens* and *J. Zizlsperger*, J. prakt. Chem. *14*, 249 (1961).

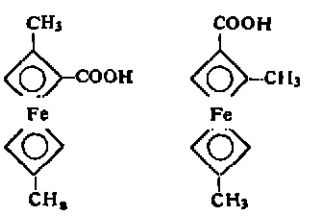
[3] *H. Behrens* and *H. Wakamatsu*, Z. anorg. allg. Chem., in the press.

[4] Investigations by *H. Behrens* and *H. Wakamatsu*, to be reported soon in Chem. Ber.

[5] Unpublished work by *H. Vogl* and *H. Passauer*.

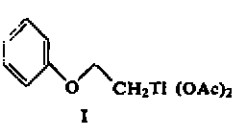
SELECTED ABSTRACTS

Resolution of 1,1'-dimethylferrocene-2-carboxylic acid (I) into its optical isomers a and b is described by *L. Westman* and *K. L. Rinehart, Jr.* Their new synthesis of I involves treatment of 1,1'-dimethylferrocene with butyl-lithium followed by carboxylation. The isomeric 3-carboxylic acid is removed by conversion into its bromobenzyl ester and chromatography on Al_2O_3. The racemate Ia,b (m.p. 108–109.5 °C) obtained on hydrolysis is treated in aqueous alcoholic solution with



solutions of alkaloids. The sparingly soluble salts obtained were purified by repeated fractional crystallization from ethanol/water, best results being obtained with cinchonidine and quinidine. Acidification of the cinchonidine fraction gives I (+), m.p. 119–121 °C, $[\alpha]_D^{25} = +37.5 \pm 1.5°$ (c = 0.8, $CHCl_3$). The quinidine fraction yields I (−), m.p. 119–121 °C, $[\alpha]_D^{25} = -36 \pm 1°$ (c = 0.8, $CHCl_3$). / Acta chem. scand. *16*, 1199 (1962) / −Br. [Rd 355/109 IE]

The oxidation of organic compounds with thallium triacetate is reported by *H.-J. Karbe*. A comparison of the reactivity of Pb(IV) acetate, Tl(III) acetate, and Hg(II) acetate on olefins, cyclohexanone, diphenylmercury, glycols, and methanol shows that Tl(III) acetate lies between the other two acetates in its reactivity. Cyclohexene and thallium triacetate in methanol produce the dimethylacetal of cyclopentylaldehyde (62 % yield), while in glacial acetic acid, the products are diacetylcyclohexanediol and 2,3-diacetylcyclopentylaldehyde (overall yield 35–50 %). In methanol, styrene yields the dimethylacetal of phenylacetaldehyde while in glacial acetic acid the product is diacetylphenylglycol (71 %). The predominant product from isobutylene is diacetatylisobutyleneglycol (27 %), as well as some acetylisobutanol (5 %). *o*-Allylphenol gives the organothallium compound I, which



I

forms α-acetoxymethylcoumaran on warming with glacial acetic acid. Two intermediates containing thallium can be isolated, which correspond with the Pb-containing intermediates postulated previously in the Pb(IV) acetate oxidation (*e.g.* $C_6H_5-CH(OCH_3)-CH_2Tl(OAc)_2$ from styrene). / Liebigs Ann. Chem. *656*, 204 (1962) / −Ma. [Rd 359/110 IE]

1,1'-Bis-(5-phenyltetrazole), the first *N,N'*-linked bis-tetrazole was synthetized by *H. Behringer* and *H. J. Fischer*. The reaction of dibenzhydrazide dichloride *(1)* with metal azides, afforded the dibenzhydrazide diazide *(2)* described by *Stolle* et al., which however showed no tendency to cyclize. With hydrazoic acid in chloroform at room temperature, *(1)* gave the hitherto unknown *N*-(5-phenyl-1-tetrazolyl)benzimide chloride *(3)* in 85 % yield, m.p. 74–75 °C. On refluxing for 3 hours with 5N KOH *(3)* gave 1-benzoylamino-5-phenyltetrazole, half of which was hydrolyzed after further 30 hours' boiling to benzoic acid and 5-phenyltetrazole. A second tetrazole ring cannot be built into *(3)* with more azide. It was therefore treated first with hydrazine hydrate to give *N*-(5-phenyl-1-tetrazolyl)benzimide hydrazide (90 % yield, m.p. 118–120 °C), which was then treated with sodium nitrite to give a 98 % yield of 1,1'-bis-(5-phenyltetrazole), (decomp. 120–121 °C). Solutions of the bis-tetrazole decompose noticeably within 30 mins. at 50 °C. Azide bands were observed intermediately in infrared spectra. One of the tetrazole rings remains intact. The diazide *(2)* is stable under these conditions and, even after 2.5 hours heating at 70 °C, 88 % can be recovered. / Chem. Ber. *95*, 2546 (1962) / W. [Rd 415/117 IE]

Protective substances excreted by insects (*Carabidae*) have been investigated by *H. Schildknecht* and *K. H. Weis*. The protective material in all the 19 species of ground beetle of the sub-family *Carabinae* investigated and in the 6 species of the sub-family *Harpalinae* investigated was identified as a mixture of methacrylic acid (87–94 %) and its next higher homologue, tiglic acid (6–13 %). In the secretion from the pygidial gland of the large water beetle (*Dytiscus marginalis* L.), *p*-hydroxybenzaldehyde and methyl *p*-hydroxybenzoate were found alongside benzoic acid; the beetle produces these for protection against microorganisms during its hibernation in the mud of dirty waters. In the protective secretion of *Oeceoptoma thorica* L., *Silpha obscura* L., and *Phosphuga atrata*, ammonia was detected as the sole volatile constituent. The excretion from the pygidium for protection of the last-named carrion beetle is mainly a 4.5 % aqueous solution of ammonia. / Z. Naturforsch. *17b*, 439, 448, and 452 (1962) / –Ho. [Rd 417/116 IE]

BOOK REVIEWS

Landolt-Börnstein, Zahlenwerte und Funktionen aus Physik, Chemie, Astronomie, Geophysik und Technik (Numerical Data and Functions in Physics, Chemistry, Astronomy, Geophysics and Technology) Vol. II. Eigenschaften der Materie in ihren Aggregatzuständen (Properties and states of matter). Part 2: Gleichgewichte außer Schmelzgleichgewichten (Equilibria other than melting equilibria). Volume Part a: "Vapour⇌condensate equilibria and osmotic phenomena". Edited by *Klaus Schäfer* and *Ellen Lax*. Springer-Verlag, Berlin-Göttingen-Heidelberg, 1960. 6th Edition, XI, 974 pp., 917 illustrations, bound. DM 448.– (about $112.00).

Another volume of this large work has appeared. A better description of its contents than that given by the book title is provided by the heading of the table of contents: "Thermomechanical constants for equilibria in heterogeneous systems". It may be supposed that its compilation was exceptionally difficult. Since the publication of the last edition, a large amount of experimental work has been carried out in this particular field, a considerable part of which has been stimulated by the needs of the chemical industry.

The first part of this volume deals with one-phase systems (330 pp.). This contains four sections: vapor pressures of pure substances; density of co-existing phases of pure substances; melting and allotropic transformations under pressure; transformation temperatures of crystalline liquids.

The longest section of the second part (430 pp.) contains vapor pressures of mixed systems. Data for 660 binary and 50 ternary systems are given as well as azeotropic points of 2800 mixtures. The remaining sections provide information about heterogeneous equilibria in which decompositions or double decompositions take place, and, furthermore, values for freezing point depression, boiling point elevation, and osmotic pressures.

The vapor pressure tables for pure substances comprise interpolated temperature data for solid pressure values between 0.1 and 760 mm. Hg. There is information about lower and higher pressures for a small number of substances. The two or three constants for each particular interpolation formula are stated. Critical data have generally been reserved for Part Volume II/1, but the data supplied in the following section for densities of co-existing phases frequently cover the whole range up to the critical point. The section on vapor pressures of mixed systems, apart from total pressure values, contains mainly equilibrium data, *i.e.* mole fractions, partial pressures, activity coefficients, and separation factors. Some of the methods used for approximation seem to be not quite satisfactory.

The literature has generally been screened up to and including 1956. However, the authors point out in the majority of chapters that even the material available up to that time could only be presented in selection. Therefore is there no claim for complete coverage, and, to some extent, the manner of selection reflects the interpretation of the particular author. Demands will inevitably differ from one group of users to the other. The requirements of chemists, however, have extensively been taken into consideration. In this sense, the section on crystalline liquids, which is certainly most interesting and which is evaluated up to 1959, perhaps exceeds the scope of the other sections. The material known up to 1956 about melting and transformation under pressure is compiled in the third section. It would be difficult to find a similarly complete recent collection of these data. On the other hand, a great deal of high pressure work has been carried out more recently, so that this chapter, if written today, would contain numerous additional transformations up to 400 kilobar. The Ba(II) ⇌ Ba(III) equilibrium pressure at room temperature, for example, which is taken as a standard, has been fixed at 59 kilobar in the meantime.

Extensive collections of data in specific fields, sponsored by interested institutions, are available at present. "Landolt-Börnstein" is still the only comprehensive compilation of tables of this kind. Thanks are due to the editor and the authors for this indispensable item in our libraries.

E. U. Franck [NB 925/30 IE]

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Cyclooligomerization of Butadiene and Transition Metal π-Complexes

BY PRIV.-DOZ. DR. G. WILKE

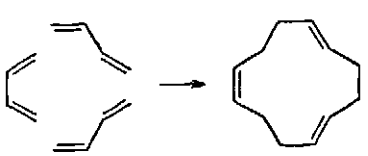
MAX-PLANCK-INSTITUT FÜR KOHLENFORSCHUNG, MÜLHEIM/RUHR (GERMANY)

BASED ON WORK DONE BY B. BOGDANOVIČ, P. BORNER, H. BREIL, P. HARDT, P. HEIMBACH, G. HERRMANN, H.-J. KAMINSKY, W. KEIM, M. KRÖNER, HERBERT MÜLLER, ERNST WILLI MÜLLER, W. OBERKIRCH, J. SCHNEIDER, J. STEDEFEDER, K. TANAKA, K. WEYER UND G. WILKE [*]

Advances in the fields of synthesis and reactions of some medium-sized hydrocarbon rings are reported and in connection therewith on novel π-complexes of transition metals. Catalytic syntheses yield 1,5,9-cyclododecatriene, 1,5-cyclooctadiene, and 1,5-cyclodecadiene either from butadiene or from butadiene and ethylene. The reactions proceed very readily.

Introduction

The work reported below originated from the surprising observation that a Ziegler-type catalyst [1,2], prepared from tetrabutyl titanate and triethylaluminum while dimerizing ethylene to 1-butene [3], readily converts butadiene into a 1,2-polybutadiene [4–6]. Thus, ethylene and butadiene react differently with the same catalyst. This prompted us to investigate the converse, *viz.* how a typical catalyst for polymerizing ethylene would behave with butadiene [7]. An experiment to prove this was carried out at the end of 1955. The catalyst was prepared from titanium tetrachloride and diethylaluminum chloride (Ti:Al = 1:4.5) in an inert hydrocarbon. This catalyst rapidly converts ethylene into polyethylene. Butadiene also reacts vigorously. However, the reaction yields a trimer of butadiene, *viz.* exclusively *trans,trans,-cis*-1,5,9-cyclododecatriene *(1)*, in yields of over 80% [8,9].



(1)

Thus, a sort of antagonism in the behaviors of ethylene and butadiene was found for the second time. However, the discovery of this extraordinarily easy synthesis of a medium-sized hydrocarbon ring was much more interesting.

It came to light later that several laboratories had at that time already investigated the behavior of butadiene and isoprene toward Ziegler catalysts. However, the objective of all these investigations was the synthesis of new kinds of rubber. The synthesis of a 1,4-*cis*-polyisoprene [10], which is to a large extent identical with natural rubber, can be mentioned as one special success resulting from such endeavors. On the other hand, these investigations showed that butadiene can also be converted into a 1,4-*trans*-polybutadiene [11] with Ziegler catalysts made from titanium tetrachloride and diethylaluminum chloride. However, the catalysts which promote

[*] The author wishes to express sincere thanks to his coworkers.

[1] These catalysts were called "organometallic mixed catalysts" by their discoverers, see *K. Ziegler, E. Holzkamp, H. Breil,* and *H. Martin,* Angew. Chem. *67*, 426, 541, 543 (1955).

[2] *G. Natta* later introduced the currently accepted term Ziegler-catalysts: Ital. Pat. 535712 (June 8th, 1954).

[3] *H. Martin,* Angew. Chem. *68*, 306 (1956).

[4] In connection with Ziegler catalysts, the structure of a 1,2-polybutadiene was discussed for the first time by *G. Natta,* Makromolekulare Chem. *16*, 213, 232 (1955).

[5] *G. Wilke,* Angew. Chem. *68*, 306 (1956).

[6] Belg. Pat. 549554, Ital. Pat. 538453 (Montecatini).

[7] *K. Ziegler* and *H. Martin,* Makromolekulare Chem. *18/19*, 186 (1955).

[8] *G. Wilke,* Angew. Chem. *69*, 397 (1957).

[9] A cyclododecatriene was first mentioned by *H. W. B. Reed;* however, the compound could not be prepared in a pure form, so that a definitive proof was not possible: J. chem. Soc. (London) *1954*, 1931.

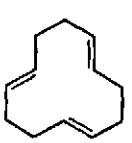
[10] *S. E. Horne, Jr., I. P. Kiehl, I. I. Shipman, V. L. Folt,* and *C. F. Gibbs,* Ind. Engng. Chem. *48*, 784 (1956).

[11] Belg. Pat. 543292 (Goodrich-Gulf Comp.).

this reaction must contain a considerably smaller proportion of diethylaluminum chloride (*e.g.* Ti:Al = 1:0.5 to 1). When this molar ratio is varied from Ti: Al = 1:0.5 to Ti:Al = 1:5, the polymers are formed in smaller and smaller amounts until finally the cyclic trimer mentioned above is obtained nearly exclusively.

The usual rules that apply for the preparation of medium-sized rings [12,13] are obviously not valid in this synthesis, *i.e.* the forces that oppose formation of medium-sized rings are either overcome by the catalyst [14] or do not appear at all during the formation of this triply-unsaturated ring (cf. the formation of cyclooctatetraene from acetylene according to *Reppe*).

Some other, occasionally even more active cyclization catalysts have been developed in the further course of our investigations (*H. Breil*). For example, a catalyst of this type is formed when diethylaluminum hydride is treated with aluminum chloride in benzene and titanium tetrachloride is then added. A suspension results, through which butadiene is passed at 40 °C and normal pressure (highly efficient cooling is necessary), cyclododecatriene being produced in 90–95% yield; a catalyst containing 1 g of titanium can convert 800–1200 g of butadiene per hour. The reaction therefore proceeds very rapidly and with high selectivity. Another active catalyst, which does not contain an organo-aluminum compound, is obtained by stirring a mixture of calcium hydride and aluminum chloride in benzene for several hours and then adding titanium tetrachloride (300–500 g of butadiene/hr per g of titanium; 80–85% yield of cyclododecatriene). Finally, a fourth catalyst (*H. Müller*), prepared from chromyl chloride and triethylaluminum in benzene, gives a mixture consisting of 60 parts of *trans,trans,trans*- and 40 parts of *trans,trans,cis*-cyclododecatriene *(2)*. The components can be easily separated, as the *trans,trans,trans*-isomer boils somewhat lower than the *trans,trans,cis*-derivative. Furthermore, it crystallizes extraordinarily well.



(2)

It should be mentioned beforehand that *cis,cis,trans*-cyclododecatriene, the third of the four possible stereoisomers, was successfully synthetized later. This compound is still not readily available and has been so little investigated that all the following data refer to only the "two isomers", *viz. trans,trans,trans*- and *trans,trans,cis*-cyclododecatriene. Some properties of the three isomers are listed in Table 1.

The configurations of these compounds can be derived from their infrared spectra, if the magnitudes of the corresponding extinctions are considered. In reporting recently that the first cyclododecatriene discovered had the *cis,cis,trans*-configuration, *Greenwood* and *Morris* [15] had obviously not taken this fact into consideration and were therefore in error.

Table 1. Properties of the three isomers of 1,5,9-cyclododecatriene

Cyclododecatriene	M.p. [°C]	B.p. [°C/10 mm]	n_D^{20}
trans,trans,trans-	+34	96	1.5005 [*]
trans,trans,cis-	−16.8	98	1.5078
cis,cis,trans-	−9 to −8	106	1.5129

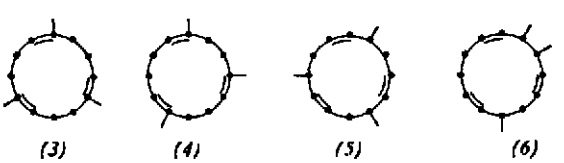
[*] Extrapolated from a series of mixtures of *trans,trans,trans*- and *trans,trans,cis*-cyclododecatriene.

The ability to add on silver nitrate is a characteristic property of both the cyclododecatriene isomers. Crystalline complexes of formula CDT·2AgNO$_3$ [*] precipitate immediately upon dropwise addition of *trans,trans,cis*-cyclododecatriene or *trans,trans,trans*-cyclododecatriene to an ethanolic solution of silver nitrate. The *trans,trans,trans*-cyclododecatriene complex can be recrystallized unchanged from ethanol, while the complex with *trans,trans,cis*-cyclododecatriene loses 1 mole of silver nitrate on recrystallization. The isomers can be recovered from the complexes by adding aqueous sodium chloride solution.

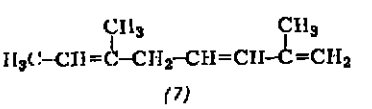
Cyclic and Open-chain Olefins from Methylbutadienes

When the experience gained from the trimerization was applied to methylbutadienes (*H. Müller, J. Kaminsky*), it became apparent that substitution of the conjugated system with methyl groups decisively influences the course of the reaction. Thus, isoprene, piperylene, and 2,3-dimethylbutadiene cannot be converted into compounds with twelve-membered rings as selectively as butadiene. Nevertheless, mixtures of stereoisomeric trimethylcyclododecatrienes *(3)* to *(6)* have been prepared from isoprene and piperylene.

With isoprene, an open-chain dimer *(7)* is formed, among other products.



(3) *(4)* *(5)* *(6)*



(7)

2,3-Dimethylbutadiene completely differs in its behaviour from the other compounds in that it gives good yields of an open-chain trimer *(8)* using the catalyst containing chromium mentioned above.

[12] *L. Ruzicka* et al., Helv. chim. Acta *9*, 249, 339, 389, 499 (1926).

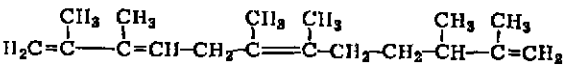
[13] *K. Ziegler* and *R. Aurnhammer*, Liebigs Ann. Chem. *513*, 43 (1934); *K. Ziegler* and *W. Hechelhammer*, ibid. *528*, 114 (1937).

[14] Principle of "cyclization with an auxiliary bond": *K. Ziegler* in: *Houben-Weyl*: Methoden der organischen Chemie. Verlag Thieme, Stuttgart 1955, Vol. IV, p. 746, 785.

[*] The following abbreviations are used in the text: CDT = 1,5,9-cyclododecatriene; COD = 1,5-cyclooctadiene; COT = cyclooctatetraene; CDD = 1,5-cyclododecadiene.

[15] *N. N. Greenwood* and *J. H. Morris*, J. chem. Soc. (London) *1960*, 2922.

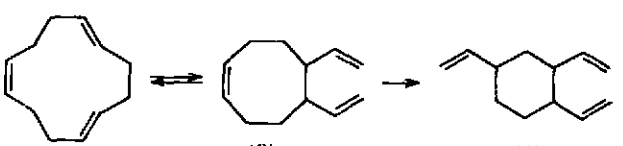
Besides initiating C–C bonding, the catalyst also promotes migration of hydrogen atoms during the formation of *(7)* and *(8)*. The structures of the resulting open-chain and cyclic compounds have been determined by degradation reactions.



(8)

Isomerization of 1,5,9-Cyclododecatrienes; Trivinylcyclohexane and Divinylcyclooctene

The two cyclododecatrienes could not be rearranged into one another using the methods conventionally applied for isomerizing olefins; they proved to be extremely stable. However, isomerization does take place when chromium (III) acetylacetonate is treated with triethylaluminum in the presence of either one of the two cyclododecatrienes, and the mixture is then heated to 200 °C. Under these conditions *trans,trans,trans*-cyclododecatriene is isomerized at a lower rate than *trans,trans,cis*-cyclododecatriene. Each isomer rearranges in part into the other. However, the main products of the rearrangement are isomeric compounds, but their constitutions are not yet precisely known. It is very probable that transannular reactions occur. It appears that *trans,trans,trans*-cyclododecatriene is the more stable isomer. Examination of the thermal stabilities of the two cyclododecatrienes was of interest in connection with the catalytic isomerization [*] [16]. Both compounds may be distilled unchanged at 20 mm through a tube filled with stainless steel wire helices and heated to 400 °C. Small quantities of new compounds were detected only above this temperature. At 500 °C, approximately 20% *trans,trans,cis*-cyclododecatriene and approximately 5% *trans,trans,trans*-cyclododecatriene were converted per run, *i.e. trans,trans,trans*-cyclododecatriene is also the thermally more stable isomer. The conversion products boil approximately 20 °C lower than the cyclododecatrienes and can easily be separated. Determination of their structures showed that the products consisted of mixtures of geometric isomers of 1,2,4-trivinylcyclohexane *(10)*.

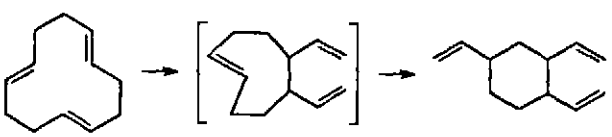


(9) *(10)*

It proved possible to adapt this reaction to a continuous process which gives yields of 90–95%. In this system, the trivinylcyclohexanes formed in a single passage were separated off immediately by distillation, while the unconverted portion was recycled. Four geometrically isomeric 1,2,4-trivinylcyclohexanes are theoretically possible, and four components have actually been detected by gas chromatography. The proof of the respective structures is based among other data on the fact that the triethylcyclohexanes obtained by hydrogenation may be converted into 1,2,4-triethylbenzene by dehydrogenation. This allowed a clear definition of the positions occupied by the three vinyl groups in the trivinylcyclohexanes.

The very uniform course of the thermal isomerization of cyclododecatriene is striking. It may be explained, however, if the first step is assumed to be a Cope rearrangement [17] leading to divinylcyclooctene *(9)*, which then rearranges to trivinylcyclohexane. The 1,2,4-positions of the substituents thus become understandable. Indeed, careful fractionation of about 5 kg of the crude product obtained from the thermal isomerization yielded ca. 100 g of a hydrocarbon boiling between 1,2,4-trivinylcyclohexane and cyclododecatriene, in all probability a 1,2-divinylcyclooctene *(9)*. Exact determination of its configuration by degradation and synthesis has not yet been achieved. However, all the properties hitherto examined are consistent with the proposed structure. The behavior of divinylcyclooctene under the conditions for thermal isomerization of cyclododecatriene is worth mentioning: it yields both *trans,trans,cis*-cyclododecatriene and trivinylcyclohexane. Thus, an equilibrium is presumably established between cyclododecatriene and divinylcyclooctene at high temperatures which is however, continuously being disrupted by the formation of 1,2,4-trivinylcyclohexane. As this second step is obviously not reversible, cyclododecatriene rearranges quantitatively into trivinylcyclohexane.

Divinylcyclooctene has so far been isolated only in the thermal isomerization of *trans,trans,cis*-cyclododecatriene. This fact may be plausibly explained by assuming that the Cope rearrangement of *trans,trans,trans*-cyclododecatriene gives a divinylcyclooctene *(11)* with a *trans* double bond in the ring.



(11)

The strain in this ring would be so great that the compound would be likely to react further immediately and thus would not be detectable in the products. By contrast, when the Cope rearrangement occurs at both of the *trans* double bonds of the cyclododecatriene, *trans,trans,cis*-cyclododecatriene forms a divinylcyclooctene with a *cis* double bond in its ring. Transformation of this divinylcyclooctene into trivinylcyclohexane proceeds at a slower rate and hence it appears in measurable quantities as an intermediate. The high temperature required (500 °C) indicates that stresses in the cyclododecatrienes do not facilitate the Cope rearrangement.

Perhydro-9b-borophenalene

Stuart-Briegleb models of 1,5,9-cyclododecatrienes can easily be constructed. In particular, the models of the *trans,trans,trans*- and *trans,trans,cis*-isomers are readily

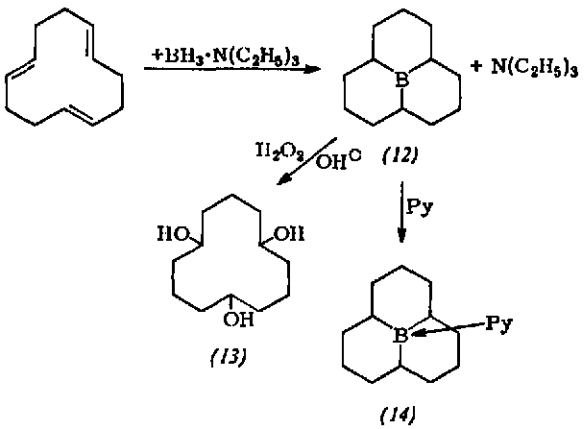
[*] These experiments were conducted in cooperation with Dr. *R. Rienäcker*.

[16] *R. Rienäcker*, Ph.D. thesis, Universität Bern, Switzerland, 1958.

[17] *A. C. Cope* and *E. M. Hardy*, J. Amer. chem. Soc. *62*, 441 (1940).

flexible. A free space can be observed in the center of both models.

In accordance with this observation, hydroboration [*] of the cyclododecatrienes and especially of the *trans,-trans,trans* isomer, *e.g.* with *N*-triethylborazane, yields a perhydro-9*b*-borophenalene *(12)*.



If it is assumed that the three valences of the boron atom also in this compound undergo sp^2-hybridization (normal trialkyl boron compounds display a trigonal-planar configuration [18]), then the center of the 12-membered ring is indeed occupied by the boron atom. This assumption agrees with the fact that the density of the "centroboron" compound ($d_4^{25} = 0.936$) is considerably higher than that of cyclododecatriene ($d_4^{25} = 0.888$) and, above all, is also higher than the densities of comparable tri-n-alkyl boron compounds. Thus the increase in molecular weight does not result in a corresponding increase of the molar volume. Provided the intermolecular forces (which could influence the density) are neglected, the density increase observed leads to the conclusion that, despite incorporation of a BH_3 molecule into the cyclododecatriene, the latter's bulk has not increased correspondingly. The simplest explanation for this is the assumption of filling of a hole previously present.

It is remarkable that both of these trifunctional compounds, cyclododecatriene and "BH_3", react to form a single monomeric compound in practically quantitative yield. *trans,trans,trans*-Cyclododecatriene seems to be just predestined for the uptake of a BH_3 molecule.

Oxidation of *(12)* with alkaline H_2O_2 solution in methanol readily yields a cyclododecanetriol (m.p. = 183.5 to 184 °C), which crystallizes well and which is obviously sterically uniform. The hydroxyl groups of this compound are most probably located at C-1, C-5, and C-9 *(13)*. The chemical behavior of the "centroboron" compound indicates that the boron atom is shielded by the surrounding ring atoms. Thus, hydrogen does not attack this compound in the presence of triethylamine at 200 °C–220 °C under pressure, whereas, under the same conditions, normal trialkyl boron compounds are split into *N*-triethylborazane and the hydrocarbon [19] from which the alkyl groups are derived. In spite of this, the fourth coordination position of the boron atom in the perhydro-9*b*-borophenalene can be occupied by electron donors, *e.g.* pyridine *(14)*, *i.e.* the boron atom can be transformed into an sp^3-hybrid, even though it is fixed in the ring.

Speculations about the Course of the Cyclododecatriene Synthesis and a First Model Experiment

The extraordinary ease of formation of cyclododecatrienes from butadiene under the influence of the catalyst systems indicated above led to speculations and experiments aimed at elucidating the course of reaction. Since these catalysts polymerize other olefins to macromolecules, the present reaction might be considered as a stepwise addition of three butadiene molecules, *i.e.*, as a normal chain polymerization in which the chain formation is interrupted by cyclization after the third step. This view assumes that the chain end always reconnects with the starting point of the chain, just as in the case of the acyloin condensation according to *Prelog* [20], where this presumably takes place on the surface of metallic sodium. However, the data which show that medium- and large-sized rings can be obtained from α,ω-difunctional, saturated polymethylenes only when the dilution principle is applied [13], indicate that such an assumption is not justified. The dilution principle must also be applied to a certain extent to the acyloin condensation. However, in this new synthesis of cyclododecatriene, the concentration of the butadiene present in the reaction is high. Butadiene can even be applied under pressure, as was recently discovered in variants of the reaction using catalysts containing nickel (see below). Nevertheless, the possibility of such a ring closure by a growing chain cannot be completely excluded. No systematic studies on the tendency of multiply-unsaturated chains to form rings are at present available.

It is possible to conceive a second course for the formation of the cyclododecatriene. According to this assumption, the active sites on the organometallic mixed catalysts which participate in the polymerization of ethylene and α-olefins [21–23] are also active in the present reaction. However, it is assumed that the present reaction differs from the polymerization in that the transition metals, which are present in their low valence states in the catalysts, will tend to fill up their electron system as much as possible in order to attain the next higher inert gas configuration. This will cause the transition metal atoms to share in the π-electron systems of the conjugated double bonds of the butadiene molecules, thus leading to the formation of π-electron com-

[*] These experiments were carried out in cooperation with Dr. *R. Köster*. The results were first made public by *R. Köster* and by *G. Wilke* in separate papers during the 16th International Congress of Pure and Applied Chemistry in Paris in 1957. See also: Angew. Chem. *69*, 684 (1957).

[18] *H. A. Levy* and *L. O. Brockway*, J. Amer. chem. Soc. *59*, 2085 (1937).

[19] *R. Köster*, Angew. Chem. *68*, 383 (1956).

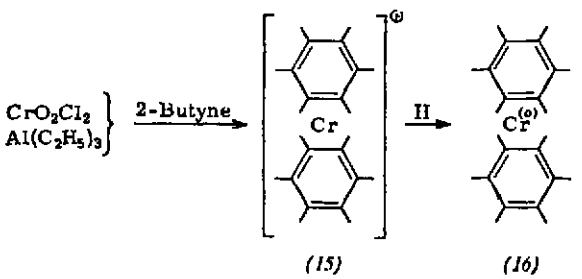
[20] *V. Prelog*, Helv. chim. Acta *30*, 1741 (1947).

[21] *D. B. Ludlum*, *A. W. Anderson*, and *C. E. Ashly*, J. Amer. chem. Soc. *80*, 1380 (1958).

[22] *W. L. Carrick*, J. Amer. chem. Soc. *80*, 6455 (1958).

[23] *G. L. Karapinka* and *W. L. Carrick*, J. Polymer Sci. *55*, 145 (1961).

plexes. The three butadiene molecules required for the formation of cyclododecatriene could thereby become arranged into a starting position favoring ring closure and moreover transferred into an activated state from which the three new C–C-bonds are formed. The C–C linking results in the loss of double bonds and therefore of π-electrons from the system. The product, cyclododecatriene, is therefore less strongly bound to the transition metal. It either detaches itself from the metal spontaneously or is displaced by fresh butadiene molecules. Experiments with nickel catalysts (see below) proved the correctness of this concept. Corresponding experimental proof for catalysts containing titanium or chromium is still lacking. However, a first model experiment with the catalyst prepared from chromyl chloride and triethylaluminum was successful. The catalyst obviously contains monovalent chromium, since, with 2-butyne, it yields the water-soluble dihexamethylbenzenechromium (I) cation *(15)*, which is transformed into dihexamethylbenzenechromium(0) *(16)* with nascent hydrogen [24]. This leads to the conclusion that six 2-butyne molecules interact with one chromium atom of the catalyst in such a manner that the electron systems of the 2-butyne molecules share the electrons of the chromium atom. Thus, two aromatic ring systems result – each based on C–C linking of three butyne molecules – which in the nascent state yield the stable arene complex [25].



(15) *(16)*

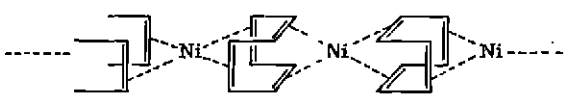
New π-Complexes of Nickel(0)

At first, these experiments with catalysts containing chromium or titanium were not followed up, because the extreme ease with which nickel yields π-complexes with olefins was recognized in the meantime. The latter complexes themselves display high catalytic activity for cyclooligomerization. A method of generally applicability for the synthesis of transition metal π-complexes was found during these investigations (*M. Kröner*). This method can also be used to prepare less stable complexes. Transition metal compounds are reduced in the presence of electron donors (particularly olefins). The reducing agents may be alkyl metal compounds (mainly alkyl aluminum derivatives) or metal hydrides. Unstable transition metal alkyls or hydrides are presumably formed as intermediates. Numerous new nickel complexes have been synthetized in this way. A crystalline yellow bis-(1,5-cyclooctadiene)nickel(0) *(17)* [26] is obtained with particular ease, using 1,5-cyclooctadiene as donor. According to its infrared and proton resonance spectra, all the double bonds of the cyclooctadiene molecules in this compound share the nickel atom, *i.e.* the nickel attains a noble gas configuration. It is not yet clear whether a tetragonal-planar *(17a)*, or a tetrahedral *(17b)* conformation is present [*]. This $(COD)_2$–Ni(0) is the first pure olefin complex of nickel(0) to have been isolated.

(17a) *(17b)*

In solution, this compound reacts with hydrogen after an induction period to form cyclooctane, highly active nickel, which is capable of catalyzing the hydrogenation of benzene at 20 °C and standard pressure, being precipitated simultaneously. Carbon monoxide displaces the cyclooctadiene from the complex, nickel carbonyl being formed in the process.

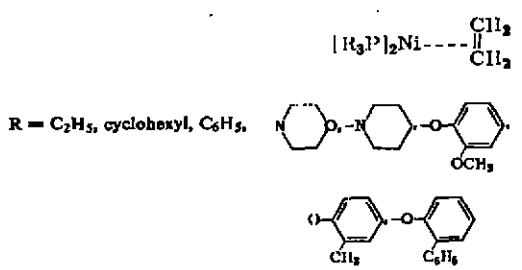
A similar complex between cyclooctatetraene and nickel has the composition COT·Ni *(18)* [26]. It forms black crystals with a metallic lustre, which are only slightly soluble but react with H_2 and CO. There is a possibility that the material is polymeric [*].



(18)

Several further examples [27] (*G. Herrmann*) are listed in Table 2. The compounds mentioned in the table, as well as the next compound to be discussed, are the first complexes known in which the nickel(0) atom is surrounded by only three ligands and can therefore have 16 electrons at the most in its outer shell. The olefinic ligands can be displaced by other electron donors in all of the compounds listed [27].

Table 2. Some new nickel(0) olefin complexes



R = C_6H_5	L = Styrene, α-methylstyrene, stilbene, tolane, 2-butyne, 1,5-cyclooctadiene
R = Cyclohexyl	L = 1-Hexene, propylene.

A complex CDT·Ni(0) *(19)*, which was prepared from cyclododecatriene and nickel by the method described above, is of special interest in connection with the cyclo-

[24] *G. Wilke* and *M. Kröner*, Angew. Chem. *71*, 574 (1959).

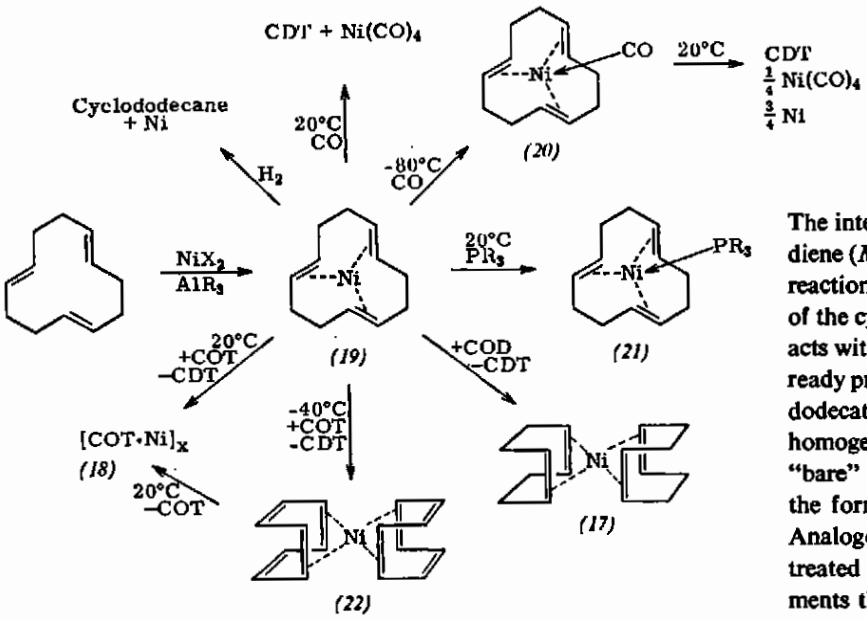
[25] Similar results were obtained by *W. Herwig, W. Metlesics*, and *H. Zeiss* in the reaction of $(C_6H_5)_3Cr{\cdot}3$ tetrahydrofuran with 2-butyne: J. Amer. chem. Soc. *81*, 6203 (1959).

[26] *G. Wilke*, Angew. Chem. *72*, 581 (1960).

[*] X-ray studies of its structure are currently in progress at the Fritz-Haber-Institut in Berlin-Dahlem (Germany).

[27] *G. Wilke* and *G. Herrmann*, Angew. Chem. *74*, 693 (1962).

trimerization of butadiene [26]. The compound crystallizes perfectly as deep red needles and can be sublimed *in vacuo*. According to its infrared spectrum, all three double bonds of the cyclododecatriene share the nickel.



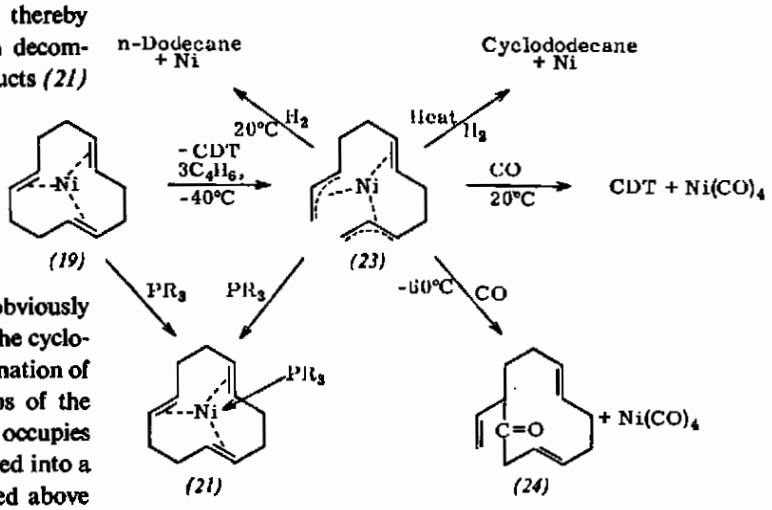
The compound is monomeric, both in the vapor phase and in solution. The nickel atom is coordinatively unsaturated, *i.e.* it attains a maximum of 16 electrons in its outer shell. The complex is extremely sensitive to air but is stable in water. In solution, it reacts immediately with hydrogen, forming cyclododecane and nickel. Its structure is similar to that of perhydro-9*b*-borophenalene *(12)*. This is also shown by the fact that the fourth coordinative position of the nickel can be filled: the complex adds on one mole of CO at −80 °C and thereby forms a white crystalline product *(20)*, which decomposes at 0 °C. However, it gives stable 1:1 adducts *(21)* with phosphines. The phosphorus atom obviously strengthens the bonds between the nickel and the cyclododecatriene, *i.e.*, it possibly promotes back donation of electrons from the metal to the carbon atoms of the double bonds. Whether the Ni atom actually occupies the center of the ring, *i.e.* whether it is hybridized into a trigonal-planar pattern, or whether it is located above the plane of the ring, cannot be decided at present. This question is going to be resolved by X-ray studies of its structure [*].

The CDT·Ni complex is ideal for studying displacement reactions [26]. The tendency of the Ni to pass from an outer shell of 16 electrons to a completely filled noble gas shell allows easy replacement of the cyclododecatriene by other ligands to be made. Thus, for example, cyclooctadiene instantly replaces the cyclododecatriene to form the $(COD)_2Ni$ *(17)* already mentioned. An analogous reaction is obtained at 20 °C with cyclooctatetraene: $[COTNi]_x$ *(18)* is the product. With an excess of cyclooctatetraene, $(COT)_2Ni$ *(22)* [28] can also be obtained at −40 °C, which at 20 °C gives $[COTNi]_x$.

Formation of Cyclododecatriene on Nickel Catalysts

The interaction of cyclododecatrienenickel(0) and butadiene (*M. Kröner, B. Bogdanovic*) is the most interesting reaction of this kind and the key for an understanding of the cyclododecatriene synthesis. Excess butadiene reacts with CDT·Ni(0) at 20 °C; the cyclododecatriene already present in the complex is displaced, and new cyclododecatriene is produced from the butadiene in the homogeneous phase in a smooth reaction. Hence, the "bare" nickel atom [**] quite unexpectedly catalyses the formation of the twelve-membered ring at 20 °C. Analogous results are obtained when $(COD)_2Ni$ is treated with butadiene at 20 °C. It was in these experiments that we obtained small amounts of *trans,cis,cis*-cyclododecatriene for the first time, in addition to *trans,trans,trans*- and *trans,trans,cis*-cyclododecatriene [28].

The cyclododecatriene is also displaced immediately when CDT·Ni(0) is treated with an excess of butadiene at −40 °C, but no new cyclododecatriene is formed. Each mole of the complex takes up exactly three moles of butadiene. A compound $C_{12}H_{18}Ni$, which crystallizes below 20 °C, was isolated from the reaction mixture.



We have assigned the structure *(23)* to it [29].

This structure is to be interpreted as follows: Three butadiene molecules assemble to give a C_{12} chain, forming a *trans* double bond and two terminal π-allyl groupings

[*] See footnote on page 109.

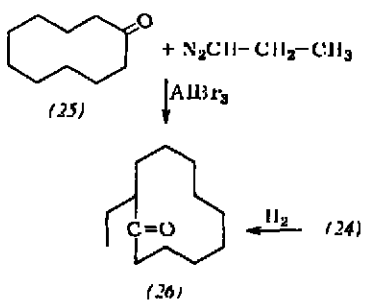
[28] *G. Wilke, B. Bogdanović, P. Heimbach, M. Kröner*, and *E. W. Müller*, Advances Chem. Ser. *34*, 137 (1962).

[**] That is, nickel present in complexes with ligands which can all be displaced by butadiene.

[29] *G. Wilke, M. Kröner*, and *B. Bogdanović*, Angew. Chem. *73*, 755 (1961).

[30–32]. The two π-electrons of the double bond, as well as the six π-electrons of the six allylic carbon atoms which are present as sp^2-hybrids, are shared by the nickel atom of the complex. We are therefore dealing formally with Ni(II). The formula scheme shows some reactions which are either consistent with this proposed structure or prove it.

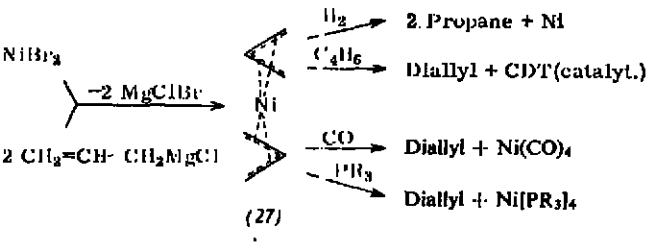
Hydrogenation of *(23)* is characteristic and affords n-dodecane in practically quantitative yields. If *(23)* is heated for a short period and hydrogenated, cyclododecane is obtained. Heating alone causes cyclododecatriene to be split off. Electron donors, *e.g.* carbon monoxide or phosphines, and butadiene have the same effect. During the reaction with phosphines, which is conducted under mild conditions in a 1:1molar ratio, the cyclododecatriene ring is closed without displacement. Products *(21)* are obtained which are identical to those prepared from cyclododecatrienenickel and phosphines. The reaction with carbon monoxide at low temperatures is especially surprising. At low temperatures, in contrast to the reaction at 20 °C, a carbon monoxide molecule is inserted into the carbon skeleton. A vinylcycloundecadienone *(24)* is obtained in good yield, along with nickel carbonyl. The constitution of the ketone was also proved by the synthesis of 2-ethylcycloundecanone *(26)* from cyclodecanone *(25)* and diazopropane, using the method of *E. Müller* et al. [33]. Compound *(26)* is identical with the compound obtained from *(24)* by hydrogenation.



Bis-(π-allyl)nickel

Finally, a particularly evident proof for the correctness of formula *(23)* is the synthesis of the bis-(π-allylnickel system. Appreciation of the fact that the outer shell of 16 electrons on the nickel is in itself sufficient for the formation of stable complexes made it probable that a bis-(π-allylnickel) complex *(27)* [formally Ni(II)] [34] might be stable as well.

This compound was, in fact, synthetized very easily from allylmagnesium chloride and anhydrous nickel bromide. It is yellow, volatile with ether, and crystallizes below 1 °C as long needles. These ignite immediately when exposed to air, but their solution in ether is quite stable towards water. Its infrared and proton resonance spectra are consistent with the structure proposed. The details of the arrangement of the two planar π-allyl systems around the nickel atom are not yet known.



The behavior of bis-(π-allyl)nickel is consistent with that of *(23)*. The bis-(π-allyl)nickel complex yields propane and elemental nickel on reduction with hydrogen. Electron donors cause coupling of the two allyl groups, yielding diallyl, a reaction analogous to the ring closure of *(23)*. Besides this, nickel carbonyl or $Ni[P(C_6H_5)_3]_4$, respectively, are formed with CO or triphenylphosphine [34]. Its reactions with cyclooctadiene or cyclooctatetraene proceed similarly. Butadiene is catalytically trimerized to cyclododecatriene. The reaction mixture also contains diallyl, which is formed in the first step. Insertion of carbon monoxide at low temperatures has not yet been practicable.

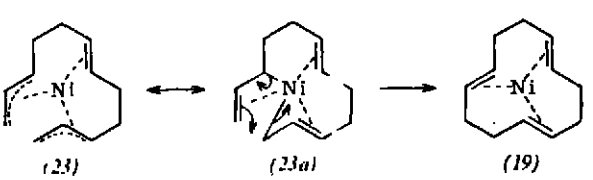
The following steps taking place on "bare" nickel during the synthesis of cyclododecatriene from butadiene have thus been proved:

1. Displacement by butadiene of ligands already adhering, but weakly bound to the nickel.

2. Linking of three butadiene molecules on the nickel, resulting in a C_{12}-chain, the ends of which are bound to the nickel in the form of π-allyl groups.

3. Ring closure under the influence of heat or preferably of electron donors and, depending on reaction conditions, formation of cyclododecatrienenickel, in which the fourth coordinative position is filled by a donor molecule.

4. Detachment or displacement of the cyclododecatriene by excess of electron donors, especially butadiene. The rate-determining step of the synthesis is the intramolecular rearrangement of the bis-(π-allyl) system, which was isolated as a reasonably stable intermediate. The rearrangement is based on rehybridization of the terminal carbon atoms in *(23)*, *viz.* $sp^2 \rightarrow sp^3$. The entire process can be described as an electron shift, using the classical formula *(23a)* [*].



[30] The first π-allyl metal compound known is the $(C_3H_5PdCl)_2$ found by *J. Smidt* and *W. Hafner*, Angew. Chem. *71*, 284 (1959). See also *I. I. Moiseev, E. A. Fedorovskaya* and *Ya. K. Syrkin*, Zh. neorgan. Khim. *4*, 2641 (1959).

[31] A π-allyl system in the form presented here was first proposed for $C_3H_5Co(CO)_3$ by *R. F. Heck* and *D. S. Breslow*, J. Amer. chem. Soc. *82*, 750 (1960).

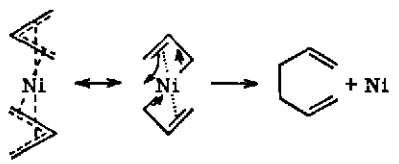
[32] A $(C_3H_5NiBr)_2$ was described by *E. O. Fischer* and *G. Bürger*, Z. Naturforsch. *16b*, 77 (1961).

[33] *E. Müller, M. Bauer*, and *W. Rundel*, Tetrahedron Letters *1960*, No. 13, p. 30; *1961*, No. 4, p. 136.

[34] *G. Wilke* and *B. Bogdanović*, Angew. Chem. *73*, 756 756 (1961).

[*] *(23a)* is only one of several possible formulae.

Formally, the valence state of the nickel should therefore constantly alternate between Ni(0) and Ni(II) during the catalysis. The intramolecular reaction step can be strongly accelerated by electron donors which interact with *(23)*. The formation of diallyl from *(27)* can be explained in an analogous manner.



(27) *(27a)*

The synthesis of cyclododecatriene on nickel is one of the few reactions in which it has become possible to follow a homogeneous catalysis closely by identifying the individual steps.

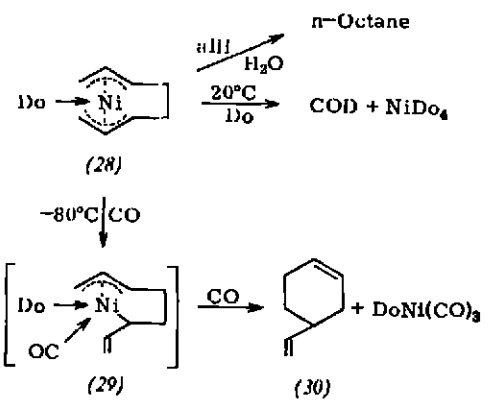
Cyclodimerization

An attempt to adapt the cyclotrimerization of butadiene into a cyclodimerization yielding 1,5-cyclooctadiene was carried out at about the same time as the investigations described in the previous section. Hitherto, two ways of forming cyclooctadiene from butadiene were known. According to *Ziegler* et al. [36,37], butadiene can be converted at approximately 300 °C into a mixture containing vinylcyclohexene and a maximum of 15% cyclooctadiene. In 1954 *Reed* [9] described a dimerization of butadiene with Reppe catalysts based on nickel carbonyl, which yielded 30–40% cyclooctadiene. The rate of reaction in *Reed*'s process is low [38].

Attempts to modify the Ziegler catalysts previously mentioned in such a manner as to cause dimerization failed at first. However, the desired modification was achieved (*E. W. Müller*) with nickel catalysts. The methods described above for preparing transition metal complexes are very suitable for the synthesis of the made-to-measure catalysts, and this brings a decisive advantage over the process according to *Reed*. Carbon monoxide, which obviously exerts an unfavorable influence on the catalysts, can now be eliminated from the start. The reaction of butadiene on nickel catalysts can be directed to yield either cyclododecatriene or cyclooctadiene. The direction of the reaction is determined by the ligands on the central nickel atom. If olefins such as cyclooctadiene or cyclododecatriene are used as complex-forming components during the reduction of a nickel compound (*e.g.* with organometallic compounds), then the catalysts produced promote virtually exclusive trimerization. The reason for this is that in these circumstances butadiene can displace all the ligands from the nickel atom, *i.e.*, it can form the intermediate complex *(23)*, thereby occupying all of the four coordination positions. The situation is similar when other weakly bonding electron donors, such as AsR_3, are present. However, the picture changes immediately when the electron donors bound to the nickel are of such a nature that they can no longer be quantitatively displaced by butadiene. In this case, some coordinative positions on the nickel remain blocked [35]. Such a complex is obtained when the nickel compound is reduced in the presence of phenylacetylene. The resulting red solution contains a catalyst which converts butadiene at 80 °C under pressure into a mixture of 8% vinylcyclohexene, 24% cyclooctadiene, and 63% cyclododecatriene. Considerably more cyclooctadiene (70%) and less trimer (ca. 10%), but still approximately 20% vinylcyclohexene are obtained with a catalyst containing triphenylphosphine instead of phenylacetylene. The same result is achieved if a solution of crystalline $Ni[P(C_6H_5)_3]_4$ is used in place of the mixture obtained in the reduction of the nickel compound. A well-defined nickel complex can therefore be used as the catalyst.

Further developments (*P. Heimbach*) then led to catalysts which convert butadiene into cyclooctadiene at 80 °C and standard pressures in yields of over 95% and at a very high rate (800–900 g of butadiene/hr per g of Ni in the catalyst). The catalyst's life is nearly unlimited, provided impurities are absolutely excluded.

In this cyclodimerization, one coordinative position of the nickel is tightly blocked by a ligand. As a result, an intermediate product *(28)* is formed which contains only two butadiene molecules.



(28) *(29)* *(30)*

The nickel atom in this intermediate complex *(28)* should have an outer shell with 18 electrons as in the intermediate complex *(23)* present in the trimerization. Cyclooctadiene could then be formed by C–C-coupling via electron shifts, just as was mentioned for *(23)*. Crystalline compounds of type *(28)*, with an open C_8-chain, have in fact been isolated. They are formed when nickel acetylacetonate is reduced at low temperatures in the presence of certain electron donors (mole ratio 1:1) and butadiene. The reaction temperature must be lowered in proportion to the catalytic activity displayed by the electron donor used in the catalytic cyclooctadiene synthesis, otherwise it is no longer the bis-(π-allyl-C_8) sys-

[35] *G. Wilke, E. W. Müller*, and *M. Kröner*, Angew. Chem. *73*, 33 (1961).

[36] *K. Ziegler* and *H. Wilms*, Liebigs Ann. Chem. *567*, 1 (1950).

[37] *K. Ziegler, H. Sauer, L. Bruns, H. Froitzheim-Kühlhorn*, and *J. Schneider*, Liebigs Ann. Chem. *589*, 122 (1954).

[38] The Reed procedure has been improved by *R. E. Burks* and *A. A. Sekul*, U.S. Pat. 2972640 and by *A. A. Sekul* and *H. G. Sellers*, U.S. Pat. 2964575, but the reaction rates are still low.

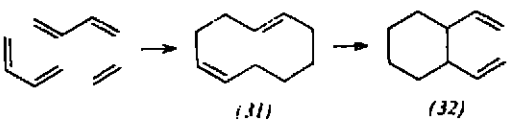
tem but already cyclooctadiene which is bound to the nickel. This is in agreement with experiments on catalysis which disclosed that not only the selectivity, but also the rate of dimerization depend on the type of donor. It is a fortunate coincidence that high selectivity and high reaction rate go hand-in-hand here. The behavior of the system with tri-(2-biphenyl)phosphite as a donor is especially clear. The compound $(RO)_3PNiC_8H_{12}$ (where R = *o*-C_6H_5–C_6H_4–) proved to be isolable in crystalline form at low temperatures. When it is warmed briefly to 20 °C and the hydrocarbon is then displaced, for example, by adding triphenylphosphine, cyclooctadiene is easily obtained. By contrast, if the complex is treated at a low temperature with an excess of diethylaluminum hydride and then heated to 20 °C, over 80% of the expected amount of n-octane is found after hydrolysis, thus proving that the ring was initially unclosed. Direct hydrogenation (as in the C_{12} series) is not successful in this case, probably owing to the presence of phosphorus compounds.

The course of the (catalytic!) formation of vinylcyclohexene *(30)* starting from *(28)* has also been clarified. This compound is formed in varying quantities, depending on the catalyst, and can even become the principal product. Vinylcyclohexene is formed in yields of over 80% if *(28)* is treated with an excess of carbon monoxide at low temperatures. This can be explained in the following manner. The carbon monoxide first breaks up one of the two π-allyl configurations, *i.e.* it takes over one coordinative position on the nickel. An electron shift coupled with a C–C coupling then takes place in the residual complex *(29)*, with simultaneous detachment of the vinylcyclohexene *(30)*. The coordinative positions which become free in this way are then filled with carbon monoxide.

These results allow the conclusion that the formation of both cyclooctadiene and vinylcyclohexene starts with the same intermediate product *(28)*. Ring closure to form cyclooctadiene prevails whenever the donors used induce a high electron mobility in *(28)*. If, on the other hand, system *(28)* has too high a stability, vinylcyclohexene is formed concurrently with the cyclooctadiene, because other donor molecules present in the reaction mixtures can cause detachment of a double bond. Selectivity with respect to the formation of cyclooctadiene and the rate of reaction must therefore go hand-in-hand, as was indeed confirmed by the catalysis experiments. According to our experience to date, the activity of the phosphorus compounds, which are the principal donors used, is determined by both electronic effects and steric factors (possibly bond angles at the phosphorus).

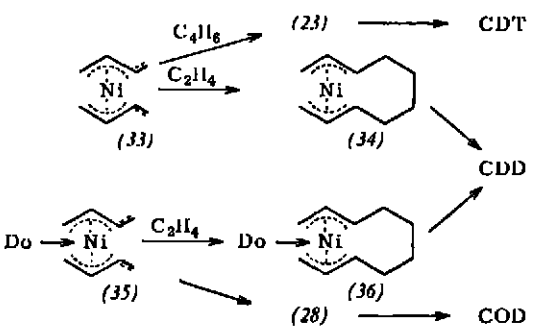
Cycloco-oligomerization; 1,5-Cyclodecadiene

On the basis of this knowledge a cycloco-oligomerization of ethylene and butadiene could be verified (*P. Heimbach*). 1,5-Cyclooctadiene and a higher boiling hydrocarbon, identified as *trans,cis*-1,5-cyclodecadiene *(31)*, are formed simultaneously and in approximately equal amounts when butadiene and ethylene react together under pressure at 60–80 °C in the presence of a catalyst suitable for the cyclooctadiene synthesis. The overall yield is approximately 95%. Cyclodecadiene is formed in a yield of 80% when butadiene and ethylene react together at a total pressure of 20 - 30 atm. and 20 °C in the presence of "bare" nickel, *i.e.* a catalyst suitable for the cyclododecatriene synthesis. The presence of ethylene therefore causes nearly complete suppression of the synthesis of cyclododecatriene which usually takes place on the nickel. The by-product of this reaction is an n-1,4,9-decatriene.



(31) *(32)*

The cyclodecane system, whose tendency to form is particularly low, becomes available for the first time in any desired amount by means of this surprisingly simple synthesis. A possible course for the synthesis of cyclodecadiene on the two catalysts is demonstrated in Scheme 1.

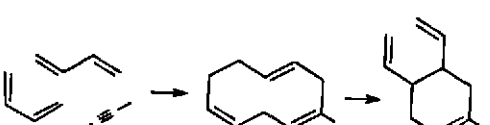


Scheme 1. Formation of cyclododecatriene (CDT), cyclodecadiene (CDD), and cyclooctadiene (COD). Do = donor.

The open-chain compound containing twelve carbon atoms *(23)* which is formed in the course of the cyclododecatriene synthesis is probably preceded by an intermediate stage *(33)* with only two butadiene molecules on the nickel. This intermediate has only a short life and is probably extremely reactive. If butadiene alone is present in the reaction mixture, then *(23)* is formed, ultimately yielding cyclododecatriene. If ethylene is also present, then almost exclusively this is incorporated possibly because of steric effects. The intermediate product *(34)* then forms cyclodecadiene.

In the cyclooctadiene synthesis catalyst *(35)*, the C–C coupling is strongly favored by the donor Do, so that the probability of insertion of ethylene becomes approximately equal to that of C–C coupling to give *(28)*. Cyclooctadiene and cyclodecadiene thus appear in equal proportions.

As expected, cyclodecadiene is a very unstable compound which is transformed quantitatively above appr. 80 °C into 1,2-divinylcyclohexane *(32)* via a Cope rearrangement. A corresponding observation was already



(37) *(38)*

made by *Grob* and *Schiess* [39] during the cleavage of a 1,5-bisquaternary base of cyclodecane.

By analogy to the reaction with ethylene, it is possible to couple 2-butyne with two molecules of butadiene to form a ring. Thus, 1,2-dimethyl-1,4,8-cyclodecatriene *(37)* is formed, which rearranges on heating to a dimethyldivinylcyclohexene *(38)*.

Further π-Allyl Compounds of Transition Metals

π-Allyl systems appear as intermediates in all the cyclooligomerizations described here. Considerable interest existed therefore in synthetizing further π-allyl compounds, both of nickel and other transition metals, with structures analogous to that of bis-(π-allyl)nickel (*P. Hardt, W. Keim, W. Oberkirch, K. Tanaka*). Some of the compounds prepared so far in crystalline form are listed in Table 3.

Table 3. Some crystalline π-allyl compounds of transition metals

Complex	Color
Bis-[π-allyl]nickel	yellow
Bis-[π-methallyl]nickel	brown-yellow
Bis-[π-crotyl]nickel	yellow
Bis-[π-allyl]palladium	straw yellow
Tris-[(π)-allyl]cobalt [*]	golden-red
Tris-[(π)-allyl]iron [*]	golden-brown
Tris-[π-allyl]chromium	deep red

[*] Since both the cobalt and the iron compounds are stable only at low temperatures, no infrared spectra are available. Therefore these compounds are listed with (π).

The π-allyl grouping is obviously a ligand system that is capable of forming well-defined, more or less stable complexes with most of the transition metals, without the necessity of having further groups, *e.g.* anions, especially halogen atoms or donor molecules such as carbon monoxide, coupled to the transition metal. Detailed investigations of this aspect are now in progress.

Cyclic Butadiene Oligomers (Co-Oligomers) as Starting Materials for Further Conversions

The novel syntheses reported in the previous sections make rings with 8, 10, and 12 carbon atoms available in an extremely easy way, starting from butadiene. It was therefore interesting to study some conventional transformations of these rings.

Reppe et al. have already investigated many of the reactions of the eight-membered ring, using cyclooctatetraene. Now 1,5-cyclooctadiene is very readily available as another starting material.

Just as with cyclooctatetraene, selective hydrogenation of 1,5-cyclooctadiene readily gives cyclooctene [36]. Starting from the latter, every monofunctional derivative of cyclooctane can be prepared, including suberic acid and capryllactam. Starting from cyclooctene, it is possible to prepare 1,7-octadiene at appr. 600 °C [40,41]. Being an α,ω-diolefin, the latter has many interesting aspects. Iron pentacarbonyl causes 1,5-cyclooctadiene to isomerize to 1,3-cyclooctadiene [42].

Corresponding investigations in the cyclodecane series are now in progress.

Completely hydrogenated cycloparaffins with 8, 10, and 12 carbon atoms are also of interest for further transformations; for example, they can be nitrated [43,44], autoxidized to cyclanones or cyclanols [45], and, according to *E. Müller* [46], may be converted directly into cyclanoneoximes with a mixture of NO, Cl_2, and HCl in a photochemical reaction. The oximes can be rearranged into caprolactam homologues with 8, 10, and 12 carbon atoms. Superpolyamides similar to Rilsan® may be obtained in this manner. These homologues of Perlon® absorb only unusually small amounts of water. In this connection the monoaldehydes or carboxylic acids of cycloparaffins which can be obtained from the cyclic olefins (mono-, di-, and trienes) by an oxo-synthesis [47] are also of interest. Using a recent process [48], these compounds can be converted directly into cyclanoneoximes or lactams.

The study of the cyclododecane group has naturally assumed the largest scope within the line of the present investigations. The preparation of monofunctional cyclododecane derivatives by way of cycloparaffins is unsatisfactory, since it appears more sensible to use the double bonds present in the starting materials. Working on this consideration, special attention has been given to the possibilities of selective reactions of cyclododecatrienes. The simplest solution would be selective hydrogenation to cyclododecene. So far, we have not been able to effect this reaction with conventional catalysts. Epoxidation [5] (*J. Schneider, K. Weyer*) of the two cyclododecatrienes, *e.g.* with peroxyacetic acid, occurs in a truly selective manner and very smoothly leads to monoepoxides (80–95% yields) without forming significant amounts of diepoxides, even at relatively high charges of reactant. This is because the second epoxidation stage proceeds approximately six times slower than the first. The *trans,trans,cis*-cyclododecatriene yields a mixture of two steroisomeric epoxides, in which the 1,2-epoxycyclododeca-*trans,cis*-5,9-diene predominates, since apparently a *trans* double bond is preferentially attacked. The monoepoxide of *trans,trans,trans*-cyclododecatriene is sterically uniform and can be crys-

[39] *C. A. Grob* and *P. Schiess*, Angew. Chem. *70*, 502 (1958).

[40] *R. Rienäcker*, Belg. Pat. 610030 (Studiengesellschaft Kohle).

[41] *A. T. Blomquist* and *P. R. Taussig*, J. Amer. chem. Soc. *79*, 3505 (1957).

[42] *J. E. Arnet* and *R. Pettit*, J. Amer. chem. Soc. *83*, 2954 (1961).

[43] Nitrocyclooctan: *W. Reppe, O. Schlichting, O. v. Schickh*, and *K. Rauch*, Ger. Pat. 932908 (BASF).

[44] Nitrocyclododecane: *G. Wilke*, Ger. Pat. 1060859 (Studiengesellschaft Kohle mbH.).

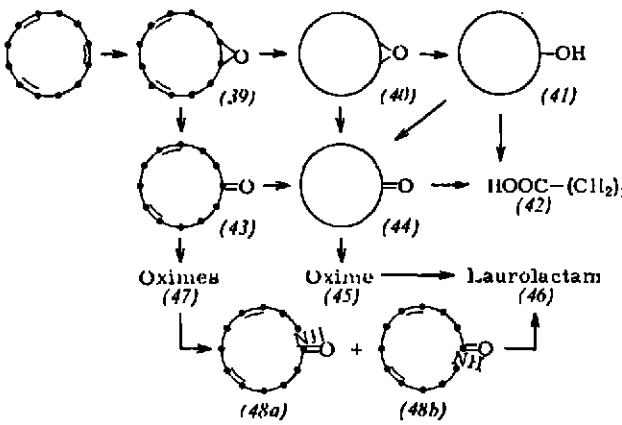
[45] See, for example, Ger. Published Pat. Application 1111177 (Société des Usines Chimiques Rhône Poulenc).

[46] *E. Müller, D. Fries*, and *H. Metzger*, Chem. Ber. *90*, 1188 (1957).

[47] Hydroformylation of cyclododecatriene: *G. Wilke* and *W. Pfohl*, Ger. Pat. 1059904 (Studiengesellschaft Kohle mbH.).

[48] Process by Snia Viscosa for producing ε-caprolactam: Nachr. Chem. Techn. *9*, 173 (1961).

tallized. The di- and triepoxides have also been prepared under more rigorous conditions. Some of the possible transformations of the monoepoxides are shown in Scheme 2.



Scheme 2. Some reactions of the monoepoxide of cyclododecatriene

It is noteworthy that both the saturated and the diolefinic epoxides can be rearranged to ketones already under extremely mild conditions by using traces of magnesium iodide (*P. Borner*).

The addition of nitrosyl chloride onto the two cyclododecatrienes, which yields mononitrosochlorides, proceeds even more selectively (*J. Stedefeder, E. W. Müller*). In each case, only a *trans* double bond reacts, the *cis* double bond of *trans,trans,cis*-cyclododecatriene remaining practically unaffected. Only the *trans*-isomers react in equimolar mixtures of *cis*- and *trans*-cyclododecene, or *cis*- and *trans*-cyclodecene, even when an excess of nitrosyl chloride is used. Model experiments with an open-chain olefin with a double bond in the middle did not proceed selectively. Thus, the selectivity observed seems to be limited to cyclic olefins, perhaps only to medium-size ones; this will be the subject of further investigations.

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Thermal Rearrangements

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The effect of conjugation with double bonds and (in cyclopropane) the effect of ring strain on the cleavage of carbon-carbon bonds during thermal rearrangements is discussed. In particular, the Cope rearrangement and the geometry of its transition state are described. The structurally degenerate Cope rearrangement of bicyclo[5.1.0]octa-2,5-diene is discussed, and this compound is used to illustrate the concept of "fluctional structure", which finds its extreme expression in the hypothetical compound, tricyclo[3.3.2.0^{4,6}]-deca-2,7,9-triene.

Introduction

One of the best known examples of a thermal rearrangements is the Claisen rearrangement, in which allyl ethers are converted by heating, via dienones, into allylphenols. A further example, which will be thoroughly treated here, is the Cope rearrangement of substituted 1,5-hexadienes. Finally, the rearrangement of cyclopropane to propene and of cyclobutene to butadiene by heating to 400 °C and 200 °C, respectively, may be mentioned.

Thermal rearrangements can be considered as consisting of two steps: bond cleavage (usually a carbon-carbon bond is opened), and recombination. It is characteristic of this process that the first step is not influenced by catalysts and is independent of the nature of the solvent. Consequently, many reactions of this type proceed just as rapidly in the gas phase as in the liquid phase. The kinetics are of the first order. The second stage of the reaction usually proceeds concurrently with the first; thus, the whole process becomes cyclic and intramolecular.

Influence of Conjugation with Double Bonds

The activation energy for the cleavage of ethane into two methyl radicals is 83.3 kcal/mole [1]. The effect of

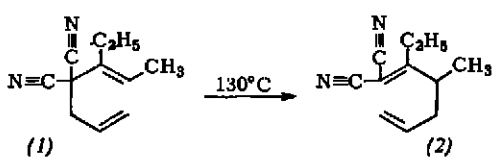
[*] Lecture delivered at the presentation of the August-Wilhelm-von-Hofmann-Denkmünze of the Gesellschaft Deutscher Chemiker on September 12th, 1962 in Munich.

[1] *T. L. Cottrell:* The Strength of Chemical Bonds. Academic Press, New York 1954, p. 201.

conjugation of the cleaved bond with a double bond can be seen from the behavior of 1-butene. Its pyrolysis yields a methyl and an allyl radical. The activation energy, 61.5 kcal/mole [2], is 21.8 kcal/mole lower than that for the cleavage of ethane. This difference is a measure of the stabilization imparted to the transition state by the delocalization of electrons in the allyl residue. The value of 21.8 kcal/mole is presumably less than the delocalization energy of a free allyl radical, since, in the rate-determining transition state of a reaction, complete electron delocalization is never attained. If the activation energy for cleavage of methyl bromide into a methyl radical and a bromine atom is compared with that for the cleavage of allyl bromide into an allyl radical and a bromine atom, a difference of 21.8 kcal/mole is obtained once more [3]; this agreement is, however, fortuitous.

It is futile to search the literature for examples in which two double bonds facilitate breaking of a carbon-carbon bond by conjugation. Investigations with 1,5-hexadiene, which should cleave into two allyl radicals, gave no clear results [4]. If the assumption is made that the effect of the double bond is additive, it may be estimated that the activation energy for cleavage of the bond between C-3 and C-4 in 1,5-hexadiene should be 39.7 kcal/mole [83.3−(2×21.8)], but this has not yet lent itself to experimental verification.

Substituted 1,5-hexadienes, such as *(1)*, are not cleaved into two allyl radicals when heated, but instead rearrange to *(2)*. This rearrangement was discovered by

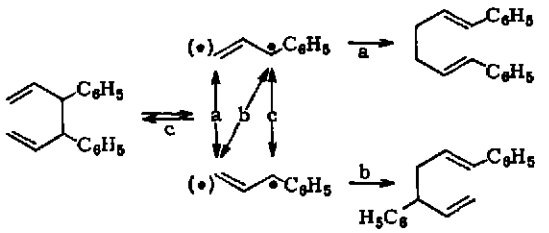


(1) *(2)*

$\Delta E_0 = +25.8$ kcal/mole
$\Delta S^{+} = -11.1$ kcal/mole

Cope [6] in 1940. It obviously has a lower activation energy than the still unknown cleavage into two allyl radicals. The Cope rearrangement also proceeds in the gas phase; it was impossible to accelerate it by change of solvent or by means of catalysts. It is an intramolecular rearrangement, with first order kinetics, and is a true thermal rearrangement of the "no mechanism" type.

A dissociation into two allyl radicals *(3)*, which could recombine in a second step in three ways (a, b, and c), was excluded for the Cope rearrangement. The type of products, the strongly negative entropy of activation, and an activation energy which is too low for a cleavage favor a cyclic, synchronous process. Instead of dissociating, the two allyl radicals are held together in a ring-shaped complex. The central question in the rearrange-



(3)

ment is the nature of this complex. How strong is the force which holds the two allyl radicals together? What is the geometry of the complex? How are the two allyl radicals arranged relative to each other?

Figure 1 shows the energy profile for the pyrolysis of 1,5-hexadiene.

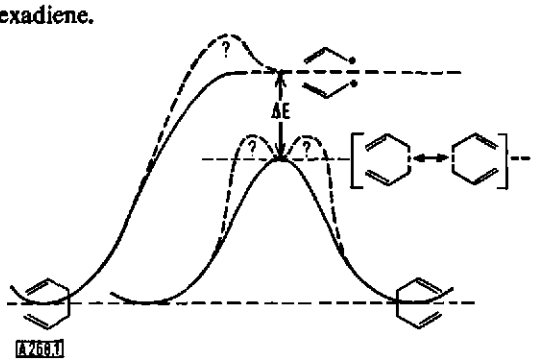
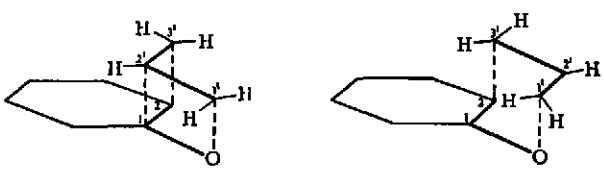


Fig. 1. Energy profile for the pyrolysis of 1,5-hexadiene with complete dissociation into two allyl radicals (upper curve) and with a Cope rearrangement (lower curve).

The upper curve represents dissociation into two allyl radicals, while the lower one represents the actual course of the Cope rearrangement. The difference in activation energy is a measure of the force which holds the two fragments together. The complex, the nature of which we wish to determine, lies at the maximum of the lower (solid) curve. It is either a transition state or an intermediate product embedded between two very similar transition states.

The question as to the geometry of the complex is equivalent to the question whether the two allyl radicals are bound together by weak binding forces between all three pairs of their atoms, or only by binding forces between the four terminal atoms. In the first case, the complex



(4) *(5)*

must have a kind of boat form (six-center arrangement), and, in the second case, a kind of chair form (four-center arrangement). In the Claisen rearrangement, it is very difficult to determine which of the two possible

[2] *H. H. Sehon* and *M. Szwarc*, Proc. Roy. Soc. (London), Ser. A *202*, 263 (1950).

[3] *A. Maccoll*, J. chem. Physics *17*, 1350 (1949).

[4] Although kinetic measurements of the pyrolysis of 1,5-hexadiene have been described [5], it is uncertain whether the activation energy (31.3 kcal./mole), which was measured by means of the decrease in diene concentration, refers to the cleavage into two allyl radicals or to the sum of different reactions.

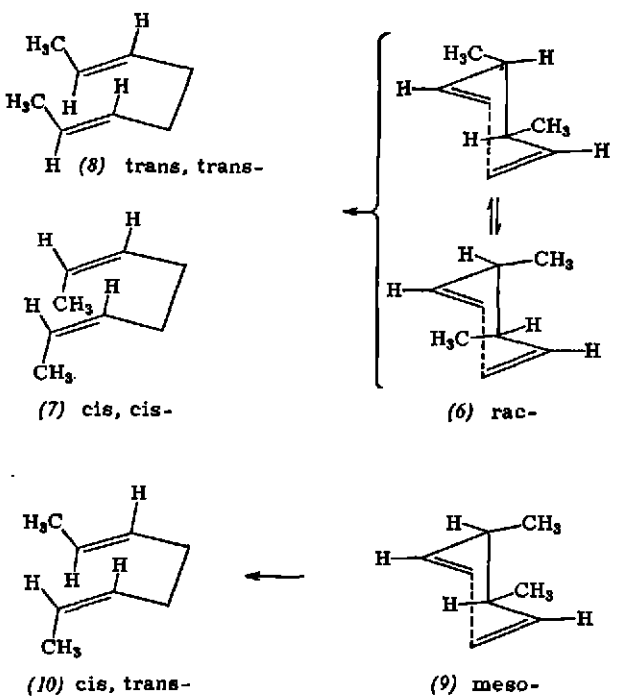
[5] *D.J. Ruzicka* and *W.A.Bryce*, J. Canad. Chem. *38*, 827 (1960).

[6] *A. C. Cope* and *E. M. Hardy*, J. Amer. chem. Soc. *62*, 441 (1940); *A. C. Cope, C. M. Hofmann*, and *E. M. Hardy, ibid. 63*, 1852(1941); *A. C. Cope, K. E. Hoyle*, and *D. Heyl, ibid. 63*, 1843 (1941); *H. Levy* and *C. A. Cope, ibid. 66*, 1684 (1944); *E. G. Foster, A. C. Cope*, and *F. Daniels, ibid. 69*, 1893 (1947).

geometries, *(4)* or *(5)*, is actually traversed. Here, the question is still open despite much, occasionally confused, speculation [7]. In contrast, an unequivocal determination can be made for the Cope rearrangement [8].

Analysis of the rearrangement of *meso*- and *rac*-3,4-dimethyl-1,5-hexadiene to the isomeric 2,6-octadienes permits conclusions regarding the geometry of the transition state. The starting materials and products are obtained by the action of magnesium on crotyl bromide. The principal product (75%) of this reaction is a mixture of *cis*- and *trans*-3-methyl-1,5-heptadiene. Along with these products, the geometric isomers of 2,6-octadiene (20%), as well as *meso*- and *rac*-3,4-dimethyl-1,5-hexadiene (5%) are also formed. The two epimers can be separated by gas chromatography, albeit with difficulty. The assignment of configurations was achieved by degradation (ozonolysis, oxidation) to *meso*- and *rac*-3,4-dimethylsuccinic acid, the configurations of which were established many years ago by the separation of the racemic compound into its optical antipodes [9]. The three geometric isomers of 2,6-octadiene, which were to be expected as rearrangement products, were obtained in pure form by gas chromatography of the synthetic mixture. The structure was assigned unequivocally by spectroscopic means.

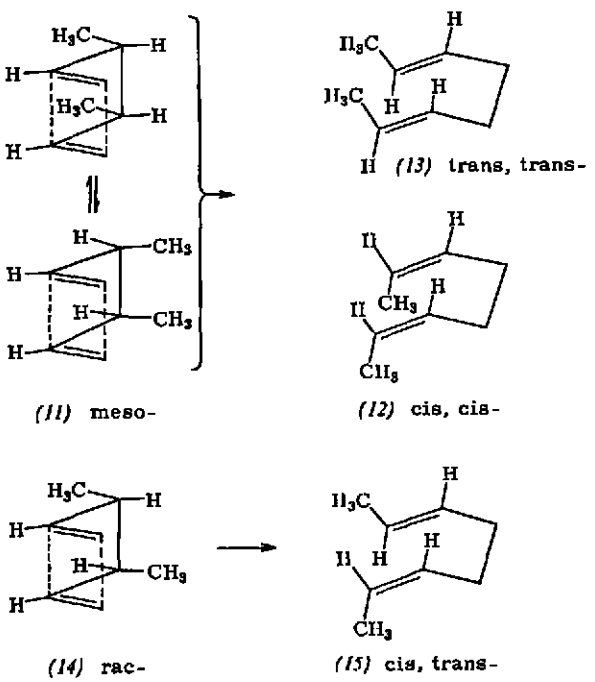
Let us first consider the result of rearrangement in the case of a four-center arrangement of the transition state (Scheme 1). *rac*-3,4-Dimethyl-1,5-hexadiene can react in two ways because of tbe orientation of its allyl triads *(6)*. The hydrogen atoms adjoining the two newly formed



Scheme 1. Products of the Cope rearrangement of 3,4-dimethyl-1,5-hexadiene with a four-center transition state.

double bonds can be oriented either *cis* or *trans* to each other in the product; *i.e.* only *cis,cis- (7)* and *trans,trans*-octadiene *(8)* can be formed. In contrast there is only one possible orientation for the epimer in the four-center transition state *(9)*, and this must lead to *cis,trans*-2,6-octadiene *(10)*.

If, on the other hand, a six-center arrangement is favored in the transition state (Scheme 2), then the *meso*-isomer *(11)* would afford a mixture of *cis,cis- (12)* and *trans,trans*-2,6-octadiene *(13)*, while the racemic isomer *(14)* must rearrange to *cis,trans*-2,6-octadiene *(15)*.



Scheme 2. Products of the Cope rearrangement of 3,4-dimethyl-1,5-hexadiene with a six-center transition state.

In actuality, *meso*-3,4-dimethyl-1,5-hexadiene rearranges at 225 °C almost exclusively (99.7%) to *cis,trans*-2,6-octadiene, *i.e.* *(9)* → *(10)*. This can occur only along the pathway via a four-center transition state. The fact that only 0.3% *trans,trans*-octadiene *(13)* is formed indicates that the difference in free energy between the four-center and the six-center arrangement amounts to at least 5.7 kcal/mole. In agreement with the conclusion drawn from the behavior of the *meso*-isomer, the *rac*-compound rearranges to a mixture of 10% *cis,cis*- and 90% *trans,trans*-octadiene, *i.e.* *(6)* → *(7)* + *(8)*; thus, this reaction also has a four-center transition state. From the preponderance of the *trans,trans*-isomer, it can be calculated that the formation of each *trans* double bond is preferred, relative to the formation of a *cis* double bond, by about 1 kcal/mole. This value lies within the order of magnitude of the known difference in the heats of hydrogenation of *cis*- and *trans*-olefins.

The preferred arrangement of the transition state is therefore the one in which only the terminal carbon atoms of the allyl radicals interact. A qualitative quantum-mechanical explanation for this fact readily suggests itself [10]. In an allyl radical, the energetically lowest molecular orbital (π_1) contains two electrons, which are distributed more or less uniformly throughout the system. When two allyl radicals are

[7] *E. R. Alexander* and *R. W. Kluiber*, J. Amer. chem. Soc. *73*, 4304 (1951); *W. N. White, D. Gwynn, R. Schlitt, C. Girard* and *W. Fife, ibid. 80*, 3271 (1958); *A. W. Burgstahler, ibid. 82*, 4681 (1960); *E. N. Marvell* and *J. L. Stevenson*, J. org. Chemistry *25*, 676 (1960).

[8] *W. v. Doering* and *W. R. Roth*, Tetrahedron *18*, 67 (1962).

[9] *A. Werner* and *M. Basyrin*, Ber. dtsch. chem. Ges. *46*, 3230 (1913).

[10] *R. S. Berry*, personal communication.

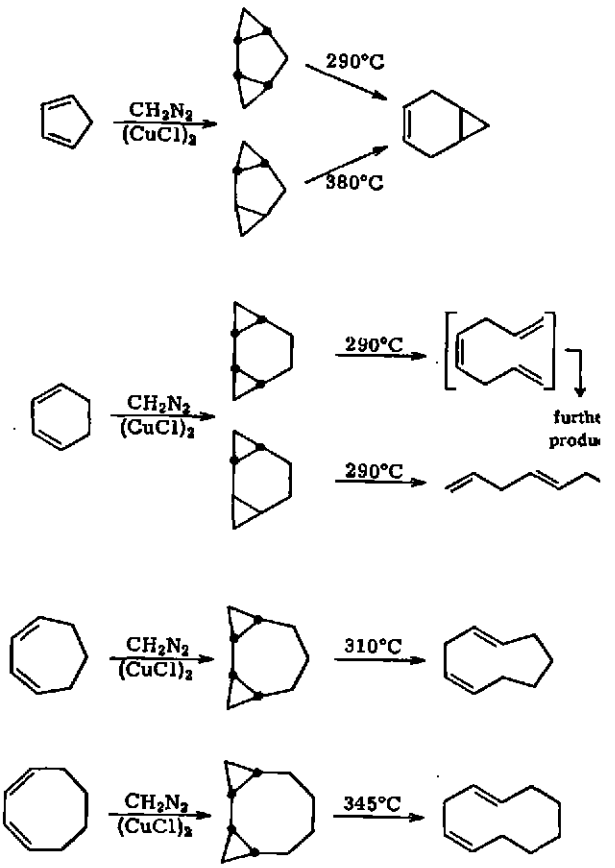
brought together, the occupied π_1 orbitals repel each other at all points. The molecular orbital of next higher energy(π_2) contains the third electron of the allyl radical and is only half occupied. Since this orbital has a vanishingly small electron density at the central carbon atom (node), two orbitals of this type can form a bond only at the terminal carbon atoms and not at the central carbon atom. The combination of the two influences has the result that the central atoms of both allyl radicals always repel each other, while bonds are possible between the terminal atoms, provided the bonding forces predominate over the repulsive forces. The four-center arrangement, with the maximum distance between the central, mutually repelling carbon atoms, therefore should be energetically favored; this is in fact the case.

Influence of Cyclopropane Ring Strain

The contribution of the ring strain in cyclopropane to the rupture of a carbon-carbon bond was elucidated by the elegant experiments of *Rabinovitch*, *Schlag*, and *Wiberg* [11]. They discovered the thermal rearrangement of *cis*-1,2-dideuterocyclopropane into its *trans*-isomer. It is quite certain that a carbon-carbon bond in the ring is broken during this reaction. There is free rotation about the remaining bonds in the diradical thus formed; ring closure then leads to either the *cis*- or the *trans*-isomer. The activation energy of the reaction is 64.2 kcal/mole. This is 19.1 kcal/mole less than that needed for the cleavage of ethane into two methyl radicals. This "assistance" of 19.1 kcal/mole is smaller than the ring strain of cyclopropane, which *Rossini* [12] determined from heats of combustion to be 27.6 kcal/mole. In the transition state for the bond cleavage, therefore, the entire ring strain is not abolished.

With regard to the extent to which two cyclopropane rings facilitate cleavage of a carbon-carbon bond, only preliminary results are known [13]. Several *cis*- and *trans*-dicyclopropyl derivatives were prepared by exhaustive cyclopropanation of cyclic 1,3-dienes (Scheme 3). The tricyclic products rearrange thermally in a smooth reaction.

Experiments with compounds labelled with deuterium show that, during pyrolysis, both cyclopropane rings are cleaved, and the central bond of the dicyclopropyl system becomes a double bond. Reactions entailing formation of a new cyclopropane ring, breaking of a carbon-carbon bond, or a transannular 1,5-shift of hydrogen lead to the rearrangement products. Rearrangements which lead to cyclic olefins with *cis* double bonds are greatly facilitated by a *cis* configuration of the cyclopropane ring in the starting material, or are even possible only with these isomers. Although a determination of the activation energies for these reactions has not been carried out, the rearrangement temperatures (about 300 °C) lead one to expect values which lie below the activation energy for the isomerization of *cis*-1,2-dideuterocyclopropane. This fact is in agreement with the hypothesis that two cyclopropane rings can co-operate provided the geometric arrangement is favorable.



Scheme 3. Rearrangements of tricyclic compounds containing two cyclopropane rings.

Simultaneous Influence of Ring Strain and Conjugation with Double Bonds

Interesting combinations of reaction facilitating effects are found in compounds in which ring strain and electron delocalization in the allyl residue act together. *Overberger* and *Borchert* [14] described the first example: the pyrolysis of vinylcyclopropane to give cyclopentene at 300 °C. If it is assumed that facilitation of reaction by ring strain and conjugation is additive, the activation energy should amount to 42.2 kcal/mole [83.3 − (21.8 + 19.1)]. *Flowers* and *Frey* [15] recently found 49.6 kcal/mole by experiment. The agreement is not particularly good, but it is good enough to suggest that the hypothesis of additivity may be useful, particularly if a standard compound more appropriate than ethane is employed.

As further examples, the racemization of α-thujene *(16)* [16] and the rearrangement of deuterium-labelled bicyclo[3.1.0]hex-2-ene *(17)* [13] may be mentioned. Both reactions are rearrangements of symmetrical vinylcyclopropanes. In the latter case, the rearrangement can be

[11] *B. S. Rabinovitch, E. W. Schlag*, and *K. B. Wiberg*, J. chem. Physics *28*, 504 (1958).

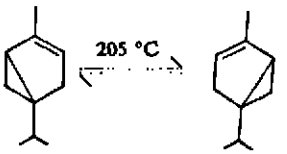
[12] *J. W. Knowlton* and *F. D. Rossini*, J. Res. nat. Bur. Standards *43*, 113 (1949).

[13] *W. v. E. Doering* and *W. Grimme*, unpublished data.

[14] *C. O. Overberger* and *A. E. Borchert*, J. Amer. chem. Soc. *82*, 1007, 4891 (1960).

[15] *M. C. Flowers* and *H. M. Frey*, J. chem. Soc. (London) 3547 (1961).

followed by the appearance of the cyclopropyl hydrogen signal in the nuclear magnetic resonance spectrum.



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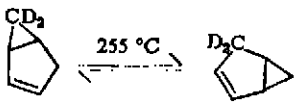
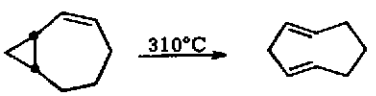


(17)

Vinylcyclopropane rearrangements involving transannular 1,5-shifts of hydrogen lead from bicyclo[5.1.0]-oct-2-ene *(18)* to 1,4-cyclooctadiene, and from bicyclo-[6.1.0]-non-2-ene *(19)* to 1,4-cyclononadiene [13].



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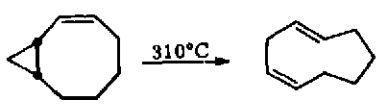

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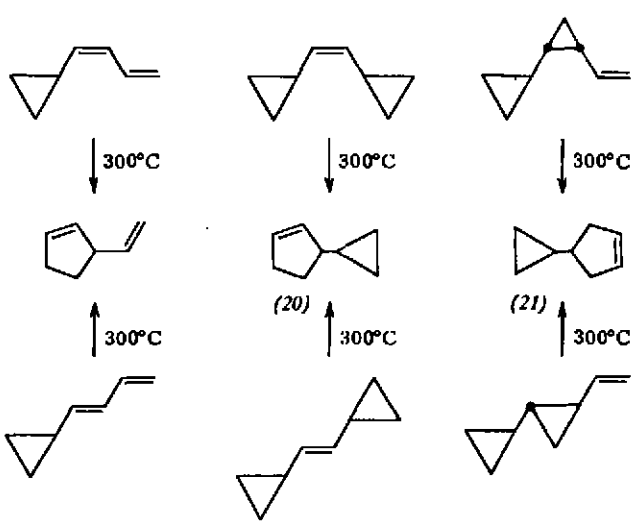
The reactions of the products obtained by mono- and dicyclopropanation of *cis*- and *trans*-hexatriene provide further examples of the vinylcyclopropane rearrangement [17] (Scheme 4). The position of the double bond in the two cyclopropylcyclopentenes *(20)* and *(21)* is still uncertain. It is interesting that no seven-membered rings are formed in this rearrangement.

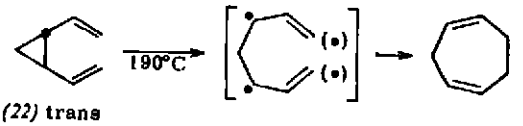
Combined facilitation of reaction by two allyl residues and a cyclopropane ring was investigated by *E. Vogel* et al. [18–20]. *trans*-1,2-Divinylcyclopropane *(22)* yields



Scheme 4. Vinylcyclopropane rearrangement of mono- and dicyclopropane derivatives of *cis*- and *trans*-hexatriene.

[16] *W. v. E. Doering* and *J. Lambert*, unpublished results.
[17] *W. v. E. Doering* and *W. R. Roth*, unpublished results.
[18] *E. Vogel*, Angew. Chem. *72*, 4 (1960).
[19] *E. Vogel*, *K.-H. Ott*, and *K. Gajek*, Ann. *644*, 172 (1961).
[20] *E. Vogel* and *R. Erb*, Angew. Chem. internat. Edit. *1*, 53 (1962).

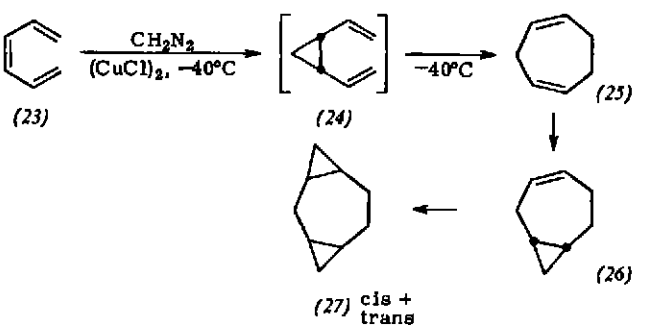
1,4-cycloheptadiene at 190 °C by a Cope rearrangement. The reaction temperature is significantly lower than that of the unfacilitated Cope rearrangement (300 °C). The large distance between the vinyl groups in *(22)* has the



(22) trans

result that two largely independent allyl radicals are formed. These then twist into a position in which the formation of the seven-membered ring can occur. A determination of the activation energy would be especially worthwhile here, since it would allow a test of the additivity rule. According to this rule, one should expect an activation energy of 20.6 kcal/mole [83.3 – (19.1 + 21.8)].

Attempts to prepare *cis*-1,2-divinylcyclopropane *(24)* invariably led to 1,4-cycloheptadiene and convinced *Vogel* [19] that here the Cope rearrangement occurs spontaneously at or below 80 °C (the temperature required for the introduction of the double bond). Our own experience leads to the conclusion that the rearrangement proceeds rapidly even at - 40 °C [21]. The mixture of products formed in the cyclopropanation of *cis*-hexatriene *(23)* at –40 °C contains, among other compounds, 1,4-cycloheptadiene *(25)* and its mono- and dicyclopropanation products, *(26)* and *(27)*.



(23) (24) (27)

If 1,2-divinylcyclopropane *(24)* is assumed to be the primary product, these results signify that the Cope rearrangement has occurred even at –40 °C.

Although the rearrangement of *cis*-divinylcyclopropane proceeds with such extraordinary speed, its transition state cannot have the preferred four-center arrangement; the structure of the reaction products can be explained only on assumption of a six-center transition state.

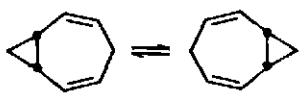
At the moment of ring closure, the two vinyl groups must adopt the sterically unfavorable *cis*-position relative to each other, although they are striving for a *trans*-orientation. If the free rotation to the *transoid* conformation is hindered, this should further accelerate the Cope rearrangement by raising the entropy of activation. One compound in which the free rotation of the vinyl groups is destroyed is bicyclo[5.1.0]-octa-2,5-diene *(28)* (3,4-homotropilidene) [21].

[21] *W. v. E. Doering* and *W. R. Roth*, Tetrahedron, in the press.

Molecules with "Fluctional Structure"

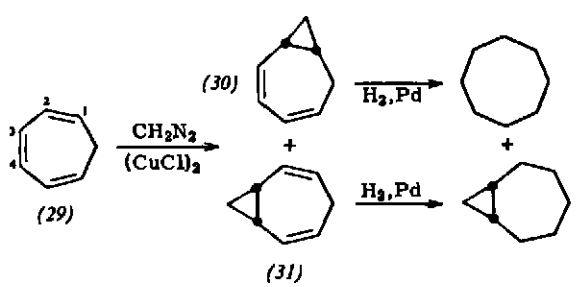
a) Homotropilidene

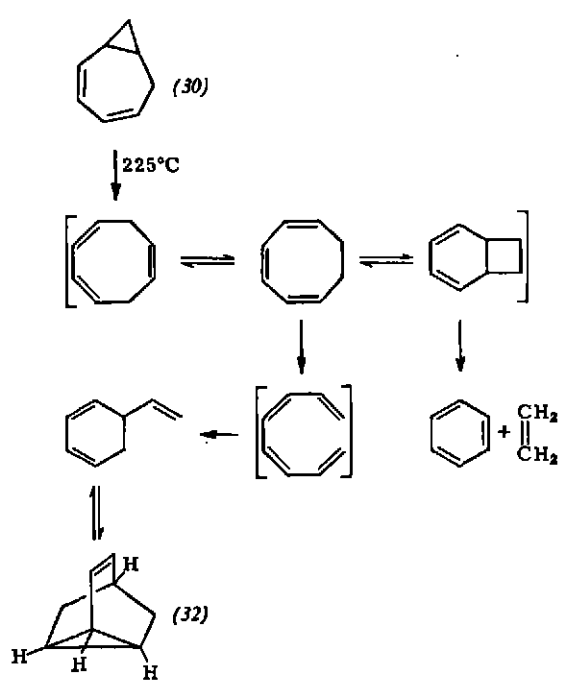
If the vinyl groups in *cis*-1,2-divinylcyclopropane are joined by a methylene bridge, the amusing consequence is that the Cope rearrangement does not produce a new substance. Instead, the starting material and the rearrangement product are now identical *(28)*: the Cope rearrangement degenerates [22].



(28)

Cyclopropanation of tropilidene *(29)* yields a mixture of 1,2- *(30)* and 3,4-homotropilidene *(31)*; these isomers can be separated by gas chromatography. Their structure follows from their ultraviolet spectra: Being a conjugated diene, the 1,2-isomer *(30)* absorbs at 258 mμ (ε = 4200), while the 3,4-isomer *(31)* shows no absorption above 215 mμ. Both can be hydrogenated catalytically to cyclooctane and bicyclo[5.1.0]octane; however, their pyrolysis products are different.

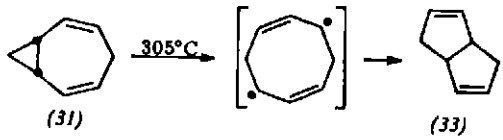




[22] This possibility was mentioned by Prof. *E. Vogel* in a lecture at Heidelberg on April 25th, 1961.

1,2-Homotropilidene *(30)* undergoes an interesting rearrangement at 225 °C: cyclooctatriene is first formed by migration of hydrogen, and this then rearranges to benzene and ethylene (as previously described by *Alder* and *Krane* [23]) and to tricyclo[2.2.2.0^{2,6}]oct-7-ene *(32)*. Compound *(32)* is formed by cleavage of cyclooctatriene to octatetraene, cyclization to vinylcyclohexadiene, and an intramolecular Diels-Alder addition.

3,4-Homotropilidene *(31)* is surprisingly stable, and does not rearrange to form different compounds below 305 °C. At 305 °C, tetrahydropentalene *(33)* is formed.



The most striking property of 3,4-homotropilidene, however, is disclosed by its nuclear magnetic resonance spectrum. The spectrum changes fundamentally with temperature (Fig. 2). At low temperatures (−50 °C), the spectrum is well resolved and has a complex fine structure. On heating, as room temperature is approached, the spectrum becomes more and more diffuse, until finally, of the ten hydrogen atoms, only the vinyl hydrogens are clearly discernible. On increasing the temperature further, a new spectrum is gradually formed, which is well characterized at 180 °C. The vinyl band at 4.3τ now has only half of its previous area, and the cyclopropane band at 9.7 τ (−50 °C) has completely disappeared. A band corresponding to four hydrogen atoms

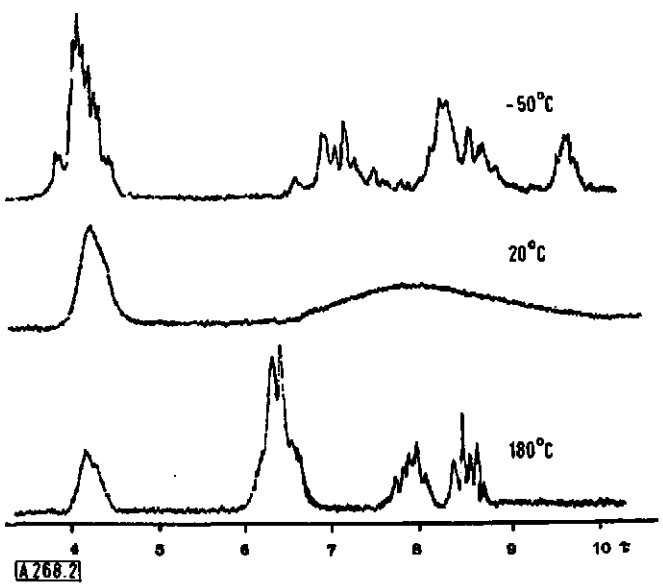


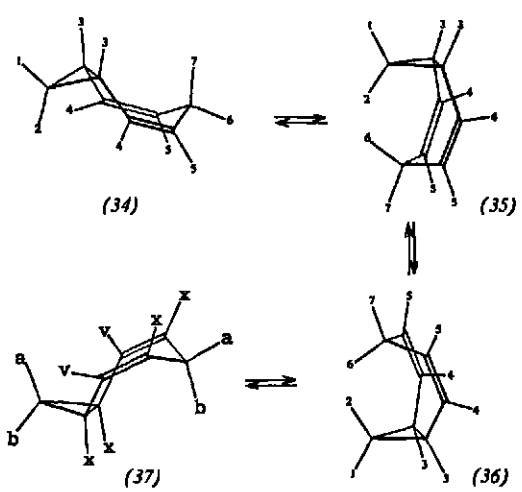
Fig. 2. Nuclear magnetic resonance spectrum of 3,4-homotropilidene at −50 °C, 20 °C, and 180 °C.

has appeared at 6.7 τ. The bands for the remaining four hydrogen atoms are somewhat symmetrically arranged around 8.3 τ. The fine structure denotes a relatively simple kind of spin-spin coupling. These changes are reversible. This gives the impression that the molecule has at low temperatures a structure different from that at higher ones. This is all the more surprising because its infrared spectrum is unchanged over the same range of temperature.

[23] *W. Krane*, Ph.D. Thesis, Universität Köln, 1960.

This apparent contradiction is due to the formation of average values. Transitions in NMR spectroscopy correspond to very low energies; in accordance with the uncertainty principle, their measurement requires a long time. If a hydrogen atom changes its place during this time, *i.e.* if its average probability of residence in a particular place is shorter than the time required for the measurement, a series of energies rather than a single defined band is observed. If, however, the change of position is sufficiently rapid to be comparable to the reciprocal of the frequency difference between the hypothetical resonance signals before and after the change of position, then a new sharp band appears in the middle of the two former end bands, which begin to disappear [24]. Thus, the significance of the NMR spectra of 3,4-homotropilidene becomes clear: at 180 °C, the hydrogens exchange places so rapidly that the mean value of the band positions is observed in the spectrum. The fact that the infrared spectrum does not change with temperature shows that the change of position does not lead to a permanent alteration of the structure. This can be explained only on the basis of a Cope rearrangement of 3,4-homotropilidene in which the starting material and the product are alike.

Consideration of models leads to the recognition of a *cisoid (35)* and a *transoid (34)* conformation for the 3,4-homotropilidene molecule; the *transoid* conformation is thermodynamically favored, since here the two methyl groups are widely separated and do not hinder each other. However, the Cope rearrangement is not possible in this conformation in the absence of a considerable activation energy. It is only when the hydrogen atoms H^3 and H^4 at each of the two newly formed double bonds lie almost in a plane with their carbon atoms right from the start that the rearrangement proceeds easily.



(34) *(35)* *(37)* *(36)*

$H^1 \equiv H^7$ 2 a
$H^2 \equiv H^6$ 2 b
$2\,H^3 \equiv 2\,H^5$ 4 x
$2\,H^4$ 2 v

In the *transoid* form *(34)*, the angle between the two hydrogen atoms is 80°. In this *cisoid* form *(35)*, it is only 10°, and is thus significantly closer to the optimum angle of 0°. In the *cisoid* form, however, considerable repulsion between hydrogen atoms H^2 and H^6 is to be expected. The *transoid* conformation is therefore thermodynamically favored over the *cisoid* conformation but in the Cope rearrangement, it has a far lower rate of reaction. This means that the infrared and NMR spectra are always those of the *transoid* form, while the isomerization proceeds *via* the *cisoid* form. In the *transoid* conformation of 3,4-homotropilidene *(34)*, seven types of hydrogen atoms are found at low temperatures: the two hydrogens (H^1 and H^2) of the methylene group of the cyclopropane ring (hydrogen H^2 absorbs at lower field strength because of its proximity to the two double bonds), the pair of tertiary, allylic hydrogen atoms of the cyclopropane ring (H^3), the two pairs of vinyl hydrogens (H^4 and H^5), and finally the two unlike methylene hydrogens H^6 and H^7. In the Cope rearrangement, which proceeds *via* the *cisoid* conformation *(35)* and which again yields a *cisoid* form, *(35)* → *(36)*, the cyclopropane hydrogen H^1 becomes methylene hydrogen H^7, while H^2 becomes H^6. Correspondingly, H^7 becomes H^1 and H^6 becomes H^2. If the rearrangement proceeds rapidly enough, H^1 and H^7 become equivalent, forming a pair of hydrogens of type a; H^2 and H^6 form a pair of type b. In the rearrangement, cyclopropane hydrogens H^3 become H^5 and vice versa. Thus, in a rapid rearrangement, a new band appears, corresponding to four hydrogens (x) centered between the vinyl and cyclopropane hydrogen bands. Only the vinyl hydrogens H^4 (v) remain unchanged in the Cope rearrangement. The spin-spin coupling is of the type abx_2. With respect to the NMR spectrum, a sufficiently rapid Cope rearrangement alters the effective symmetry of 3,4-homotropilidene: a molecule which has seven kinds of hydrogen atoms at low temperatures becomes a system with only four types of hydrogen at higher temperatures.

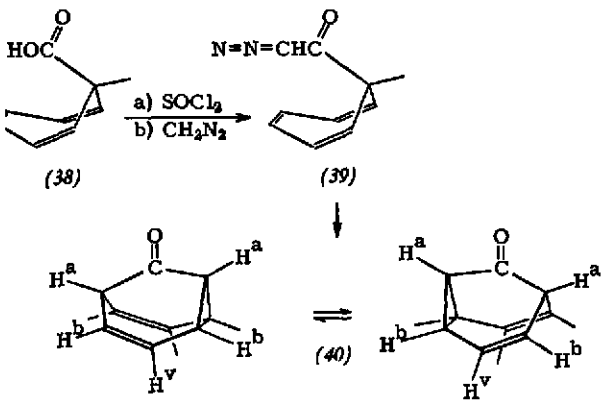
At high temperatures, the number of vinyl hydrogens in the NMR spectrum in the region of 4.3 τ has decreased from four (two H^4 and two H^5) to two (H^v). At a temperature that is only slightly higher, these vinyl hydrogens are recognizable as a triplet (H^v split by two H^x). A new band, corresponding to four hydrogens of type x, appears at 6.4 τ, the average between 4.3 τ (two H^5) and 8.5 τ (two H^3). A band system with almost mirror symmetry, corresponding to four hydrogens (two H^a and two H^b), is centered about 8.2 τ; this is characteristic of the ab portion of an abx_2 spectrum.

It can be estimated that 3,4-homotropilidene undergoes the Cope rearrangement about one thousand times per second at 180 °C, and about once per second at −50 °C. This is the first definite example of an organic molecule which must be described as the mean between two identical structures. It may be said of such molecules that they have a "fluctional structure".

The Cope rearrangement of 3,4-homotropilidene proceeds rapidly. It seemed possible that it would perhaps be even faster, if the kinetically unfavorable *transoid* conformation were excluded. This was achieved by incorporating a third bridge between C-4 and C-8 in 3,4-homotropilidene [25]. Starting out from norcaradiene-carboxylic acid *(38)*, a diazoketone *(39)* was formed

[24] *J. A. Pople, W. G. Schneider,* and *H. J. Bernstein:* High-resolution Nuclear Magnetic Resonance. McGraw-Hill, New York 1959.

with diazomethane *via* the acid chloride and then treated with copper to yield a ketocarbene with evolution of nitrogen. This carbene does not rearrange to a ketone as in the Arndt-Eistert synthesis, but instead, it adds here onto the 3,4-double bond to give a tricyclic ketone *(40)*.

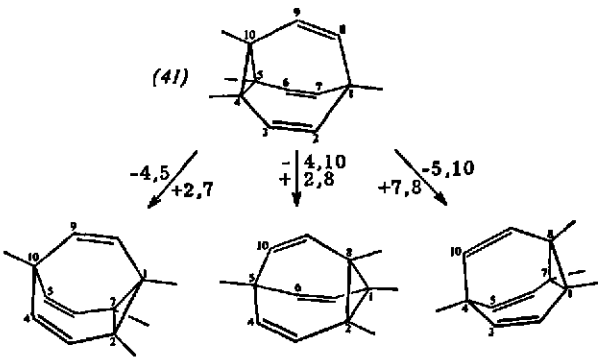


The NMR spectrum of this ketone remains unchanged on cooling to −60 °C, and can only be interpreted as an average of hydrogen positions in consequence of a rapid Cope rearrangement.

The signals of the two vinyl hydrogens (H^v) appear at 4.3 τ and are split by the neighboring pair of type b hydrogens to form a triplet. Each portion of the triplet is resplit by the transannular hydrogens of type b. The hydrogens of type a appear in the NMR spectrum as a perfect triplet, split by the neighboring hydrogens of type b. The band of the four equivalent hydrogens (centered around 5.8 τ) is split in a complicated manner by H^a, the two hydrogens H^v, and by the transannular hydrogen pair H^b. This molecule too can be described only by averaging two classical structures; it is an especially impressive example of this new type of substance with a "fluctional structure".

b) "Bullvalene"

The extreme example of such a molecule is the hypothetical compound tricyclo[3.3.2.0^{4,6}]deca-2,7,9-triene *(41)* ("bullvalene"). The molecule is theoretically formed from 3,4-homotropilidene by connecting the secondary cyclopropane carbon to the methylene group by a further double bond. It corresponds to the tricyclic ketone *(40)*, but with the difference that the carbonyl bridge is replaced by an ethylene bridge. The structure has a threefold axis of symmetry. If the Cope rearrangement were to proceed here as rapidly as with the tricyclic ketone *(40)*, bullvalene had only one type of hydrogen atom. Three reversible Cope rearrangements, the products of which are alike because of the threefold axis of symmetry transform the cyclopropane atoms C-10, C-5, and C-4 successively into bridgehead atoms. At the same time the carbon atoms adjacent to the bridgehead (C-1) become cyclopropane carbons (C-7 and C-2, C-8 and C-2, C-7 and C-8). By further rearrangements, these also become bridgehead atoms. In the first series of rearrangements, carbon atoms C-9, C-6, and C-3 become atoms adjoining the bridgehead atom. Such atoms first become cyclopropane atoms, and then are transformed in a second rearrangement to bridgehead atoms. Thus, if C-1 is the bridgehead atom, the carbon atoms C-4, C-5, and C-10 are only one Cope rearrangement removed from



becoming bridgehead atoms themselves. The carbon atoms C-2, C-7, and C-8 are twice-removed from the bridgehead position, and the carbon atoms C-9, C-6, and C-3 require three rearrangements. In other words, all the hydrogen atoms have, on the average, the same position, and only a single sharp band is to be expected in the nuclear magnetic resonance spectrum.

However, the most surprising property of this hypothetical substance bullvalene is not so much the prediction of only one NMR band, but rather the fact that all its isomers can be transformed into one another. With ten carbon atoms, there are more than 1.2 million combinations that form bullvalene. The most unusual property of this molecule is that each of these arrangements can be transformed into any other one by Cope rearrangements. If bullvalene has only a single hydrogen band in the NMR spectrum, it follows that all the 1.2 million possible arrangements appear simultaneously. The carbon atoms do not remain bound to each other in a fixed arrangement, but move statistically on the surface of a spherical molecule. Despite this extreme fluctuation, however, the structure of bullvalene does not change.

It might be asked whether the borderline between mesomerism (or resonance) on the one hand and tautomerism on the other does not vanish in a molecule such as bullvalene. Group theory gives an unequivocal answer. Ten points cannot be arranged on the surface of a sphere so as to form a completely symmetrical, three-dimensional figure. Our phenomenon would therefore be one of tautomerism and not of mesomerism.

[25] *W. v. E. Doering* and *B. Ferrier*, unpublished data.

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Fulvenes as Isomers of Benzenoid Compounds

BY PROF. DR. K. HAFNER, DR. K. H. HÄFNER, DR. C. KÖNIG, DR. M. KREUDER, DR. G. PLOSS, CAND. CHEM. G. SCHULZ, CAND. CHEM. E. STURM, AND DR. K. H. VÖPEL

CHEMISCHES INSTITUT DER UNIVERSITÄT MARBURG/LAHN (GERMANY) AND INSTITUT FÜR ORGANISCHE CHEMIE DER UNIVERSITÄT MÜNCHEN (GERMANY)

With regard to the nature of their bonding and reactivity, fulvenes occupy a position intermediate between their benzenoid isomers and the olefins. The chemical and physical behavior of the fulvenes is determined either by the diene character of the cross-conjugated system or by the cyclic conjugation in the five-membered ring, depending on the type of substituent at the exocyclic carbon atom. In addition to several new substitution reactions, a description is given of the syntheses and reactions of 6-amino- and 6-hydroxyfulvenes, isomeric with anilines and phenols, the derivatives of which can be used for the preparation of new types of nonbenzenoid cyclic conjugated systems such as carbocyclic and heterocyclic azulenes, pseudoazulenes, thiepines, dihydropyridazines, and s-indacene.

Introduction

In connection with the question of the nature and origin of "aromatic character", recent interest has centered chiefly on nonbenzenoid cyclic conjugated compounds. The cyclopentadienyl anion *(1)* [1] and the tropylium cation *(2)* [2], although discovered at the turn of the century, have acquired within the last decade special significance as the parent structures of a multitude of "quasiaromatic" systems, as a consequence of the suggestion, more than thirty years ago, by *Robinson* [3] and *Ingold* [4] and especially *Hückel* [5] of the close relationship to benzene engendered by the common π-electron

(1) *(2)*

sextet. The realization, that various carbocyclic nonbenzenoid compounds might possess aromatic character – earlier *Bamberger* [6], indicated the benzene-like behavior of several five-membered heterocycles and interpreted this as being due to the presence of six "potential valences" – stimulated the preparation of many new types of carbocyclic and heterocyclic conjugated nonbenzenoid systems and led to investigations of the relationships between their structures and their chemical and physical properties as a means of obtaining further information on the correlation between constitution and "aromatic character" [7].

In this respect, special importance must be allocated to compounds which are isomers of benzene and its derivatives, namely the fulvenes *(3)*. These cross-conjugated systems were prepared for the first time by *Thiele* [8] at the turn of the century by condensing cyclopentadiene with aldehydes and with ketones in the presence of bases. Their dipole moments of approx. 1.5 D [9] and the resonance energy of the cross-conjugated system of about 12 kcal/mole [10] (nearly one-third of the resonance energy of benzene) indicate their intermediate position between benzenoid and olefinic compounds.

Day [11] and *Bergmann* [12] have reviewed the progress of fulvene chemistry up to 1955. In the present paper, we shall report only the results of our own investigations. These results reveal with unusual clarity contrasting and common features of the benzenoid and fulvenoid systems.

Fulvenes as Nonbenzenoid Cyclic Conjugated Systems

The nature of the bonding in fulvenes *(3)* can be described qualitatively as a mesomeric superposition of the covalent structure A and the polar structure B. The contribution of the dipolar structure B to the resonance

[1] *J. Thiele*, Ber. dtsch. chem. Ges. *34*, 69 (1901).

[2] *G. Merling*, Ber. dtsch. chem. Ges. *24*, 3108 (1891); *W. v. E. Doering*, and *L. H. Knox*, J. Amer. chem. Soc. *76*, 3203 (1954).

[3] *J. W. Armit* and *R. Robinson*, J. chem. Soc. (London) *127*, 1604 (1925).

[4] *C. K. Ingold* and *E. H. Ingold*, J. chem. Soc. (London) *1926*, 1310.

[5] *E. Hückel*, Z. Physik *70*, 204 (1931); Grundzüge der Theorie ungesättigter und aromatischer Verbindungen. Verlag Chemie, Berlin 1938.

[6] *E. Bamberger*, Ber. dtsch. chem. Ges. *24*, 1758 (1891); Liebigs Ann. Chem. *273*, 373 (1893).

[7] Reviews: *W. Baker* and *J. F. W. McOmie*, in *J. W. Cook:* Progress in Organic Chemistry. Butterworths, London 1955, vol. 3, p. 44. *D. Ginsburg:* Non-Benzenoid Aromatic Compounds. Interscience, New York 1959; *W. v. E. Doering:* Theoretical Organic Chemistry. Butterworth, London 1959; *M. E. Vol'pin*, Russian Chem. Reviews *29*, 129 (1960).

[8] *J. Thiele*, Ber. dtsch. chem. Ges. *33*, 666 (1900).

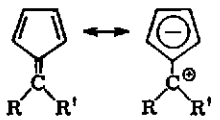
[9] *G. W. Wheland* and *D. E. Mann*, J. chem. Physics *17*, 264 (1949); this value applies to 6,6-dialkylfulvenes.

[10] *J. H. Day* and *Ch. Oestreich*, J. org. Chemistry *22*, 214 (1957).

[11] *J. H. Day*, Chem. Reviews *53*, 167 (1953).

[12] *E. D. Bergmann* in *J. W. Cook:* Progress in Organic Chemistry. Butterworth, London 1955, vol. 3, p. 81.

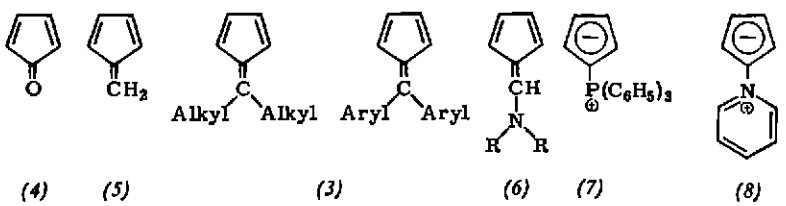
of *(3)* in the ground state amounts to only 5–10%, as may be assessed easily from the dipole moments [9] of 6,6-dialkylfulvenes and 6,6-diarylfulvenes. This contribution is larger in the excited state and is responsible for a de-



A *(3)* B

R = R' = H, Alkyl, Aryl

crease in the energy difference between the excited and ground state, and thus for the fact that fulvenes absorb at long wavelengths (compared with isomeric benzenoid systems). With the increasing electron-donating character of a substituent at carbon atom 6, the polar structure B becomes more significant [13,14]. This can be explained in accordance with Hückel's rule [5] by stabilization through the cyclic conjugated system of six π-electrons, which is present in this structure just as it is in cyclopentadienyl-metal compounds [1] and in cyclopentadiene ylides [15]. In agreement with this concept, the bond character of the fulvenes can be shifted either towards the olefinic or towards the "cyclic conjugated" side by variation of the substituents at carbon atom 6. The effect of substituents on the "aromatization tendency" of the cross-conjugated system can be studied in this manner.



(4) *(5)* *(3)* *(6)* *(7)* *(8)*

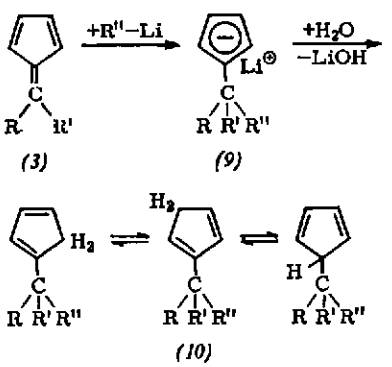
Increase in cyclic conjugation

The complete replacement of carbon atom 6 by electron-attracting atoms or groups leads to fulvenoid systems with pronounced diene properties. A characteristic representative of this group is cyclopentadienone *(4)* [16], which undergoes a Diels-Alder condensation with itself in the nascent state. On the other hand, exchange of carbon atom 6 for electron-releasing atoms or groups results in nearly complete cyclic conjugation within the five-membered ring. This is manifested in the benzene-like behavior of cyclopentadiene ylides [15] of the type *(7)* and *(8)*. The fulvenes themselves may be placed between these two fulvenoid systems, which differ so strongly in their fine structures. Depending on their degree of polarization, the fulvenes more or less combine the properties of both extremes. This applies to fulvene itself *(5)* [17] as well as to 6,6-dialkyl- or 6,6-diarylfulvenes *(3)*, and fulvenes containing functional groups at carbon atom 6, *e.g. (6)*. Of these compounds, the 6,6-dialkyl- and 6,6-diarylfulvenes and the parent compound itself *(5)* have been especially well characterized. The latter is apparently thermally unstable and very susceptible to autoxidation. The readiness of fulvenes to undergo Diels-Alder reactions, both as dienes and dienophiles, to add on halogens, and to form peroxides (all characteristic olefinic properties) have been reported.

Being cyclic conjugated isomers of benzenoid compounds, these cross-conjugated systems may also undergo substitution reactions. Some of the fulvene derivatives thus obtained strongly resemble the isomeric benzene derivatives and prove to be valuable starting materials for the synthesis of both known and novel polycyclic conjugated nonbenzenoid compounds.

Substitution Reactions Involving 6,6-Dialkylfulvenes and 6,6-Diarylfulvenes

Besides the tendency to 1,4-additions already mentioned, which is due to the pronounced olefinic character of fulvenes alkylated or arylated at carbon atom 6 *(3)*, the fulvenes also undergo reactions with nucleophilic and electrophilic reagents which reveal the participation of the polar structure B. Thus, organolithium compounds add to fulvenes as first observed by *Ziegler* and coworkers [18]. In agreement with calculations of its elec-



(3) *(9)*

(10)

[13] *G. Kresze* and *H. Goetz*, Chem. Ber. *90*, 2161 (1957).

[14] *K. Hafner*, Angew. Chem. *74*, 499 (1962); *K. H. Häfner*, Ph. D. thesis, Universität Marburg, 1962.

[15] *D. Lloyd* and *J. S. Sneezum*, Chem. and Ind. *1955*, 1221; Tetrahedron *3*, 334 (1958); *F. Ramirez* and *S. Levy*, J. org. Chemistry *21*, 488 (1956); J. Amer. chem. Soc. *79*, 67 (1957).

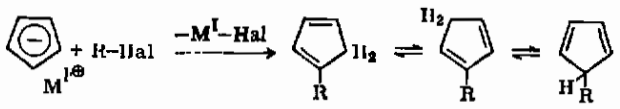
[16] *K. Hafner* and *K. Goliasch*, Chem. Ber. *94*, 2909 (1961); *C. H. DePuy*, *M. Isaks* and *K. L. Eilers*, Chem. and Ind. *14*, 429 (1961); *C. H. DePuy*, *B. W. Ponder* and *J. D. Fitzpatrick*, Angew. Chem. *74*,489 (1962) and previous publications; *E. Vogel* and *E.-G. Wyes*, *ibid. 74*, 489 (1962).

[17] *J. Thiele* and *H. Balhorn*, Liebigs Ann. Chem. *348*, 1 (1906); *J. Thiec* and *J. Wiemann*, Bull. Soc. chim. France *1956*, 177; *1957*, 366; *1960*, 1066; see also *H. J. F. Angus* and *D. Bryce-Smith*, J. chem. Soc. (London) *1960*, 1409.

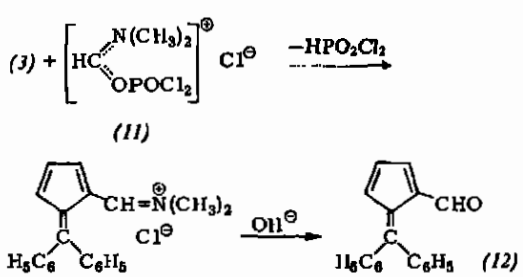
[18] *K. Ziegler*, *F. Croessmann*, *H. Kleiner*, and *O. Schäfer*, Liebigs Ann. Chem. *473*, 1 (1929); *K. Ziegler* and *W. Schäfer*, *ibid. 511*, 101 (1934); see also *D. Lavie* and *E. D. Bergmann*, Bull. Soc. chim. France *18*, 250 (1951); *R. C. Fuson* and *F. E. Mumford*, J. org. Chemistry *17*, 255 (1952); *R. C. Fuson* and *O. York*, *ibid. 18*, 570 (1953); *D. Taber*, *E. J. Becker*, and *P. E. Spoerri*, J. Amer. chem. Soc. *76*, 776 (1954); *A. G. Bonagura*, *M. B. Meyers*, *S. J. Storter*, and *E. J. Becker*, *ibid. 76*, 6122 (1954).

tron density distribution [19], the nucleophilic reagent attacks the fulvene at the exocyclic carbon atom to form an alkylcyclopentadienyl-lithium compound *(9)*.

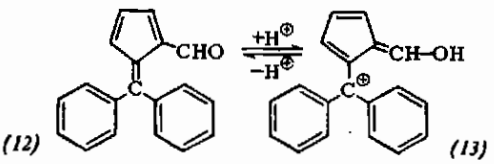
The driving force behind this reaction is the gain in resonance energy originating from the transition of the cross-conjugated system to the cyclic conjugated state. Metal hydrides react similarly with these fulvenes [20]. Hydrolysis of *(9)* leads to alkylated cyclopentadienes *(10)*. Thus, alkylating or arylating reduction of the exocyclic double bond supplements the synthesis of substituted cyclopentadienes from cyclopentadiene- metal compounds and alkyl halides [21].



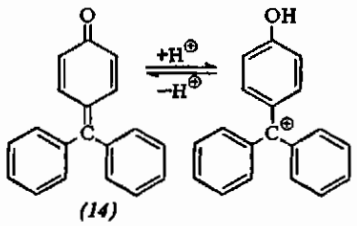
Electrophilic substitution in fulvenes has not attracted much attention, since such experiments have so far been of doubtful success [22]. In fact, however, fulvenes are as susceptible to electrophilic substitution as other nonbenzoid cyclic conjugated compounds. Thus, 6,6-diphenylfulvene *(3)*, R = R′ = C_6H_5, is formylated with ease and in high yield by treatment with Vilsmeier's complex *(11)*, obtained from dimethylformamide and phosphorus oxychloride [23,24]. Again, in accordance with the theoretically derived electron density distribution [19], the electrophilic reagent attacks at carbon



atom 2 of the cross-conjugated system to yield the aldehyde *(12)*, the structure of which has been confirmed by its nuclear magnetic resonance spectrum (ABX). This stable red fulvenaldehyde resembles its isomer fuchsone *(14)*. Like the latter, it is readily and reversibly protonated at the carbonyl oxygen to give the conjugated acid *(13)*. The ultraviolet spectrum of aldehyde *(12)* largely resembles that of the fuchsone.

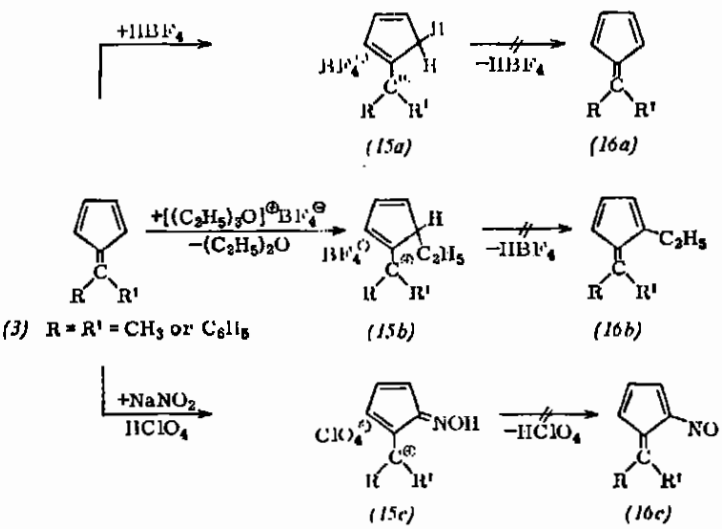


λ_{max} = 250 mμ (log ε = 4.28)
346 mμ (log ε = 4.18)



λ_{max} = 252 mμ (log ε = 4.35) [25]
360 mμ (log ε = 4.50)

6,6-Diphenylfulvene and 6,6-dimethylfulvene *(3)*, R=R′=CH_3, also undergo protonation, alkylation, and nitrosation at temperatures as low as −80 °C [14], σ-complexes of type *(15)*, which are stable only at −80 °C,



being obtained first as colorless salts. The conversion of these fulvenium salts into substituted fulvenes *(16)* has not yet been accomplished, polymeric products *(18)* being formed instead. Ionic polymerization of the possible intermediary 1,3-dipole *(17)* probably competes with the conversion of the carbonium salts *(15)* into the cross-conjugated substitution products *(16)*, since this change is associated with only a slight energy gain. *Thiec* and *Wiemann* [17] observed a similar polymerization with unsubstituted fulvene.

Moreover, the dark red polymethine dye salts *(19)* and *(20)*, which are obtained respectively from the fulvenium salts *(15a)* and benzaldehyde and from 6,6-diphenylfulvene-2-aldehyde *(12)* by an acid-catalyzed

[19] *G. Berthier* and *B. Pullmann*, Bull. Soc. chim. France [4] *16*, D 461 (1949).

[20] *K. Ziegler*, Angew. Chem. *64*, 323 (1952); *K. Ziegler, H. G. Gellert, H. Martin, K. Nagel*, and *J. Schneider*, Liebigs Ann. Chem. *589*, 91 (1954); *K. Hafner*, *ibid. 606*, 79 (1957); Angew. Chem. *70*, 419 (1958); *H. Dohm*, Ph. D. thesis, Universität Marburg, 1958.

[21] *K. Alder* and *H. Holzrichter*, Liebigs Ann. Chem. *524*, 145 (1936); *H. Dohm*, Ph. D. thesis, Universität Marburg, 1958; *R. Riemschneider* and *E.-B. Grabitz*, Mh. Chem. *89*, 748 (1958); *R. Riemschneider* and *R. Nehring*, *ibid. 90*, 568 (1959).

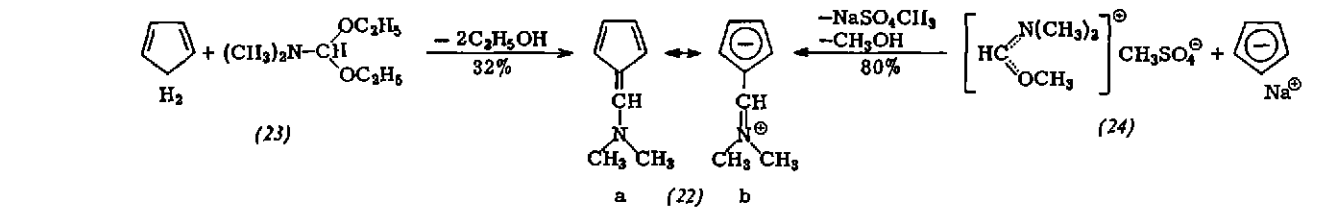
[22] *E. Bergmann* and *A. v. Christiani*, Ber. dtsch. chem. Ges. *63*, 2559 (1930); *64*, 1481 (1931); *J. H. Day* and *C. Pidwerbesky*, J. org. Chemistry *20*, 89 (1955).

[23] *A. Vilsmeier* and *A. Haack*, Ber. dtsch. chem. Ges. *60*, 119 (1927); *Ch. Jutz*, Chem. Ber. *91*, 850 (1958); *H. H. Bosshard* and *Hch. Zollinger*, Angew. Chem. *71*, 375 (1959); Helv. chim. Acta *42*, 1659 (1959); *H. Bredereck, R. Gompper, K. Klemm*, and *H. Rempfer*, Chem. Ber. *92*, 837 (1959).

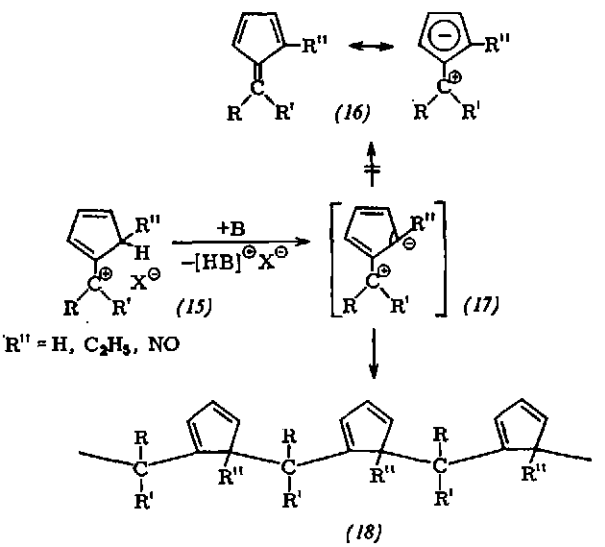
[24] *K. H. Vöpel*, Ph. D. thesis, Universität Marburg, 1960; *K. Hafner* and *K. H. Vöpel*, Angew. Chem. *71*, 672 (1959); *K. Hafner*, *ibid. 72*, 574 (1960).

[25] *E. Walton, A. F. Wagner, F. W. Bachelor, L. H. Peterson, F. W. Holly*, and *K. Folkers*, J. Amer. chem. Soc. *77*, 5144 (1955).

aldol condensation [*] polymerize rapidly under the action of nucleophilic reagents. This behavior indicates that the sextet stabilization of the fulvenes forming the basic structure of the fulvenium salts *(15)*, *(19)*, and *(20)* is weak. Thus, these salts differ from their benzenoid isomers and from other nonbenzenoid cyclic conjugated systems, *e.g.*, azulene [26] and 6-aminofulvenes, which give addition products that often rearrange spontaneously into cyclic conjugated systems.



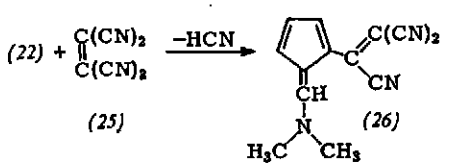
(23) *(22)* a b *(24)*



(16) *(15)* *(17)* *(18)*

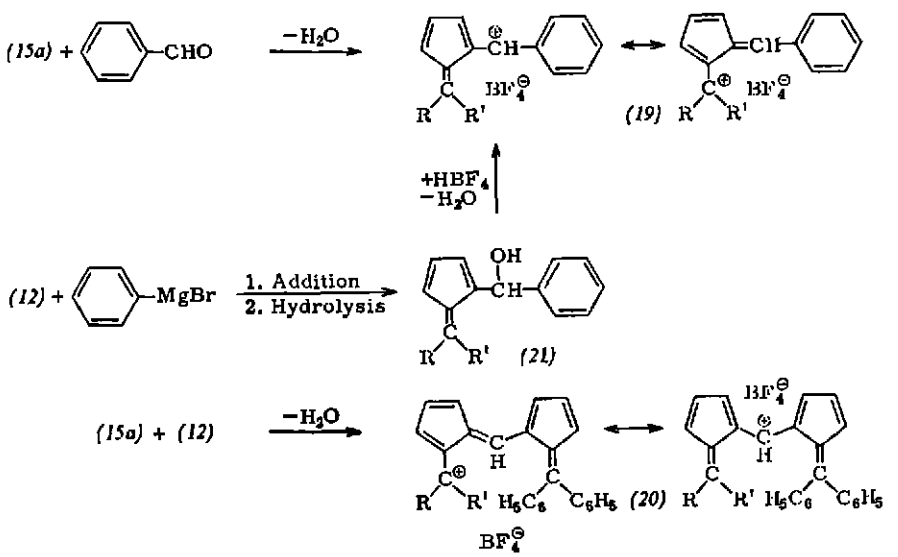
6-Amino- and 6-Hydroxyfulvenes

Fulvenes with functional groups at carbon atom 6 have only very recently become known. *Meerwein* and coworkers [27] were the first to succeed in preparing 6-(dimethylamino)fulvene *(22)*; they obtained it by condensing *N,N*-dimethyldiethoxymethylamine *(23)* (which they discovered) with cyclopentadiene. We also obtained this fulvene, which is an isomer of and chemically similar to *N,N*-dimethylaniline, in over 80 % yield by treating cyclopentadienylsodium with the carbonium immonium methosulfate *(24)* [28], prepared from dimethylformamide and dimethyl sulfate. Its dipole moment of 4.5 D [29], indicates that there is considerable participation (approx. 25 %) of the dipolar cyclic conjugated structure *(22b)* in the ground state; this explains the slight tendency of this fulvene to behave as a 1,3-diene. Electrophilic substitution at the five-membered ring proceeds readily. Thus, just like its benzenoid isomer, this compound adds on tetracyanoethylene *(25)* to yield 2-tricyanovinyl-6-dimethylaminofulvene



(25) *(26)*

(26) [30] and, on acylation, gives mono- and diacyl derivatives. Moreover, the slight solvatochromism exhibited by solutions of *(22)* when nonpolar n-hexane is replaced by water as solvent indicates a strong polarization corresponding to structure *(22b)*. On the other hand, vinylogous fulvenes *(27)*, n = 1–3, which are readily acces-



(19) *(21)* *(20)*

[*] The product *(19)* may also be obtained by the reaction of the fulvenaldehyde *(12)* with phenylmagnesium bromide, yielding the carbinol *(21)*.

[26] *K. Hafner*, Angew. Chem. *70*, 419 (1958).

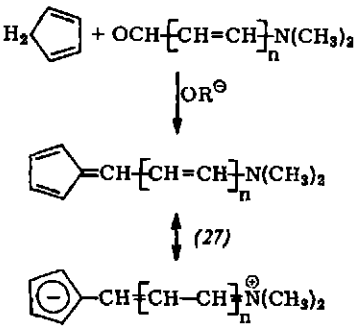
[27] *H. Meerwein, W. Florian, N. Schön*, and *G. Stopp*, Liebigs Ann. Chem. *641*, 1 (1961).

[28] *H. Bredereck, F. Effenberger*, and *G. Simchen*, Angew. Chem. *73*, 493 (1961).

[29] *K. Hafner, K. H. Vöpel, G. Ploß*, and *C. König*, Liebigs Ann. Chem. *661*, in the press.

[30] *G. Schulz*, diploma thesis, Universität München, in preparation.

sible from cyclopentadiene and ω-dimethylaminopolyenals, show considerable increases in solvatochromism with increasing n. This is especially evident in the shifts



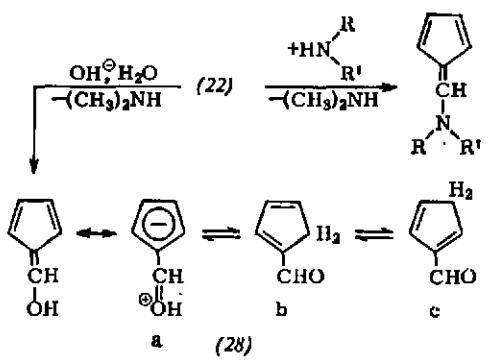
of the absorption band of longest wavelength (Table 1) and is to be attributed to the transition of these fulvenes to a polar excited state [31].

Table 1. Absorption spectra of vinylogous aminofulvenes *(27)*

Aminofulvene *(27)*	Main absorption band [mμ (log ε)] in			
	n-hexane	methanol	formamide	methanol/ H_2SO_4 (1 %)
n = 0	316 (4.49)	322 (4.52)	326 (4.49)	318
n = 1	375 (4.67) 242 (3.70)	401 (4.68) 244 (3.79)	419	376 239
n = 2	411 (4.75) 261 (3.70)	445 (4.71) 267 (3.72)	481	422 270
n = 3	429 (4.79) 280 (3.71)	464 (4.76) 283 (3.73)		433 286

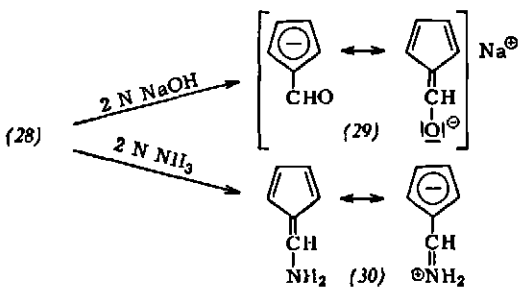
In contrast to *(22)*, the vinylogous aminofulvenes *(27)* are thermally unstable; this, in conjunction with some of their reactions, points to a stronger 1,3-diene character and, thus, to a weaker sextet stabilization for them. At the same time, this finding shows in an impressive manner the limitations of the vinylogue principle [32].

The fulvene *(22)* reacts with nucleophilic reagents exclusively at the exocyclic carbon atom, *e.g.* with primary or secondary amines with exchange of the amino group or with hydroxyl ions to yield 6-hydroxyfulvene *(28)* [30], which is isomeric with phenol. From its infrared and NMR spectra, *(28)* appears to exist as a mixture of



a *(28)* b c

tautomeric forms *(28a, b,* and *c)*. This is the simplest fulvene isolated so far; it is only slightly stable thermally and is susceptible to autoxidation. Although the pK_α value of *(28)* is equal to that of phenol, the unionized compound has largely the nonpolar cross-conjugated structure and only a slight resonance contribution from the dipolar structure. While phenol is cyclically conjugated only in its enolic form, the fulvenoid isomer is conjugated only in its anionoid carbonyl form. This explains why the sodium salt of 6-hydroxyfulvene is more stable than the free fulvene. With bases – even with 2N sodium hydroxide – the fulvne *(28)*is rapidly transformed to the energetically favored formylcyclopentadienyl anion *(29)*. 6-Hydroxyfulvene, like other hydroxymethylene compounds, reacts with 2N ammonia to give the stable 6-aminofulvene *(30)* which, like aniline, readily undergoes electrophilic substitution; it has thus established itself as a starting material for the synthesis of many new fulvene derivatives [30].



6-Aminofulvenaldehydes

6-Dimethylaminofulvene *(22)* and its derivatives not only have a propensity for nucleophilic exchange reactions at carbon atom 6, but are also highly reactive toward electrophiles. The fulvene *(22)* reacts even at −60 °C with the Vilsmeier complex *(11)* to yield the immonium salt *(31)*, which can be isolated as its perchlorate or iodide. Hydrolysis of *(31)* with alkali leads to 6-dimethylaminofulvene-2-aldehyde *(32)* [29,33]. On the other hand the fulvene *(22)* reacts rapidly at 20 °C with two molecules of the formylation reagent *(11)* to give the symmetrical bis-immonium salt *(33)*, which is extensively stabilized by resonance. Hydrolysis of *(33)* with alkali yields 6-dimethylaminofulvene-3,4-dialdehyde *(34)*, a fulvene derivative isomeric with *N,N*-dimethylamino-*o*-phthaldialdehyde. At the same time, the isomeric 6-dimethylaminofulvene-2,4-dialdehyde *(35)* is also formed in low yield, apparently in dependence on the conditions of hydrolysis.

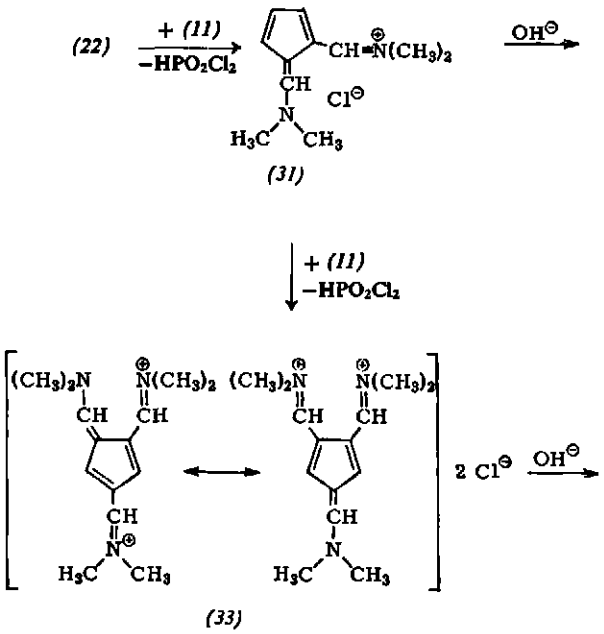
Both fulvenaldehydes are obtained in a simpler manner directly from cyclopentadiene and the Vilsmeier complex *(11)*. Thus, the cyclic 1,3-diene reacts even at −20 °C with the electrophilic reagent to yield, probably, the addition product *(36)*, which by elimination of one mole of hydrogen chloride and one mole of dichloro-

[31] *K. Hafner, G. Schneider,* and *W. aus der Fünten,* unpublished results; see also *K. Hafner,* Liebigs Ann. Chem. *606,* 79 (1957).

[32] Compare with corresponding observations with 6-phenylfulvenes substituted in the benzene ring, *G. Kresze* and *H. Goetz* [13]; *G. Kresze, S. Rau, G. Sabelus,* and *H. Goetz,* Liebigs Ann. Chem. *648,* 51 (1961), and with 6-furfurylfulvene and its vinylogues, *C. H. Schmidt,* Chem. Ber. *90,* 1352 (1957).

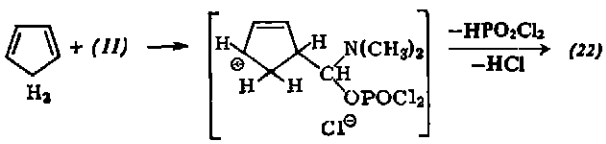
[33] *G. Ploß,* Ph. D. thesis, Universität Marburg, 1961.

phosphoric acid is then converted into the resonance-stabilized fulvene *(22)*. The latter then undergoes electrophilic substitution at position 2 in a fast subsequent step. Above 0 °C, the immonium salt *(31)* formed reacts



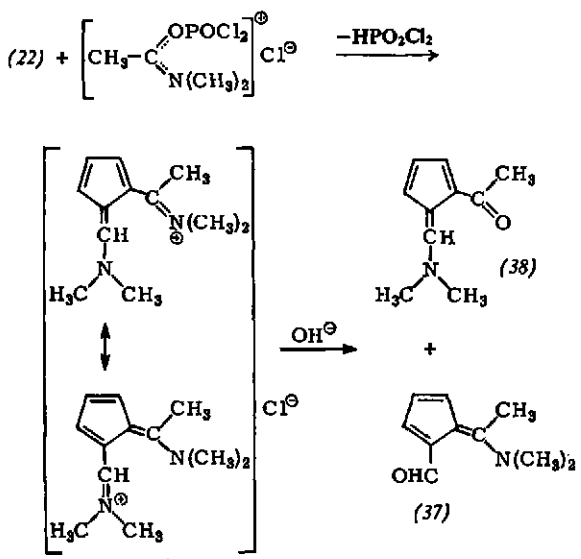
(31) *(33)*

immediately with an additional mole of the Vilsmeier complex *(11)* to give the bis-immonium salt *(33)* in over 90% yield. Thus, it is possible to obtain in good yields both the fulvenemonoaldehyde *(32)* and the fulvenedi-



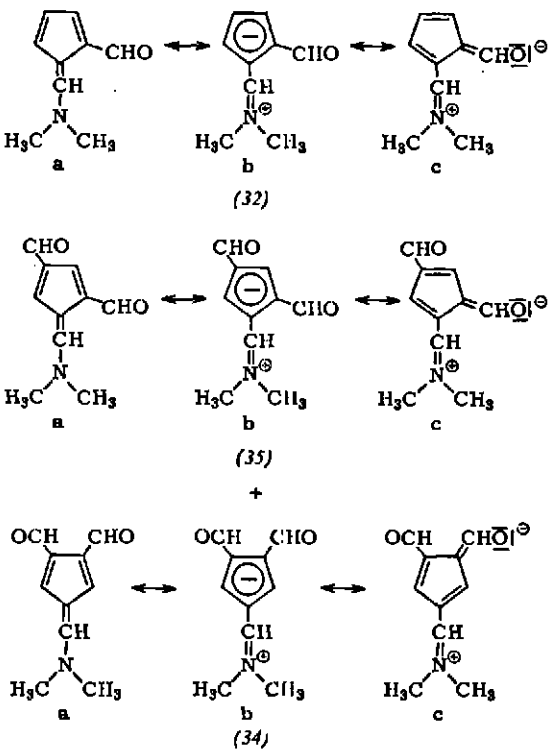
(36)

aldehyde *(34)* or their immonium salts directly from cyclopentadiene, dimethylformamide, and phosphorus oxychloride, phosgene, thionyl chloride, or other acid



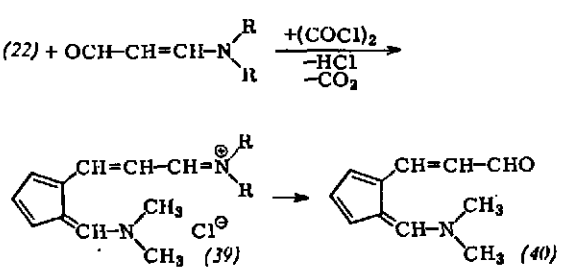
(36) *(37)* *(38)*

chlorides. Mono- or poly-alkylated or -arylated cyclopentadienes, as well as indene, also react to yield the corresponding five-membered substituted 6-(*N,N*-dialkylamino)fulvenemono- and dialdehydes [24,29,34].



(32) *(35)* *(34)*

Instead of dimethylformamide, other *N,N*-dialkylformamides may also be used for this reaction with cyclopentadiene, but not the amides of homologous carboxylic acids [14,24,29]. On the other hand, 6-(*N,N*-dimethylamino)fulvene *(22)* reacts smoothly with the Vilsmeier complex obtained from *N,N*-dimethylacetamide and phosphorus oxychloride to give the immonium salt *(36)*, hydrolysis of which then leads to a mixture of the fulvenaldehyde derivative *(37)* and the methylfulvene ketone *(38)* [30]. Compound *(22)* reacts with vinylogous amides, *e.g.* β-(*N,N*-dialkylamino)acroleins, in the presence of oxalyl chloride to give immonium salts of type *(39)*, which hydrolyze to give 6-(*N,N*-dialkylamino)-



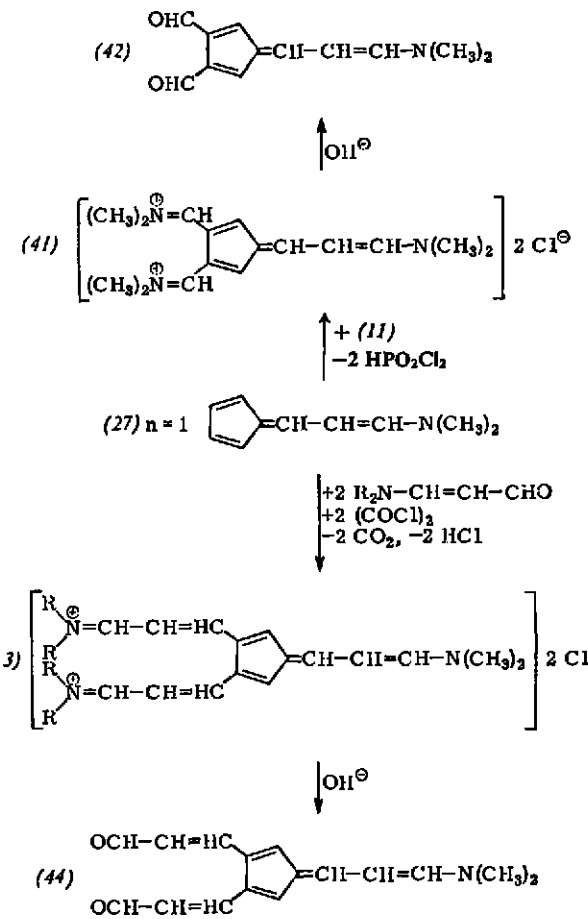
(39) *(40)*

fulvene-2-prop-2′-en-1-al *(40)* [35]. Vinylogous aminofulvenes *(27)* also undergo electrophilic substitution at the five-membered ring. Thus, formylation of the fulvene derivative *(27)* where n = 1, with the Vilsmeier complex *(11)* leads directly to the red fulvenedialdehyde *(42)*.

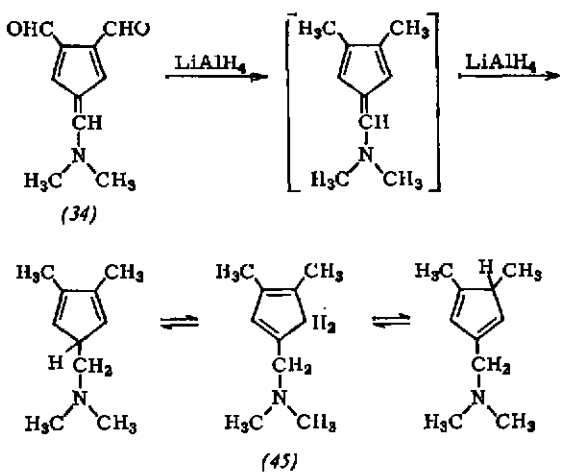
[34] After we had published these results *Z. Arnold*, Coll. Czechos. chem. Commun. *25*, 1313 (1960), also reported the reaction of cyclopentadiene with Vilsmeier's complex.

[35] *M. Kreuder*, Ph. D. thesis, Universität Marburg, 1961.

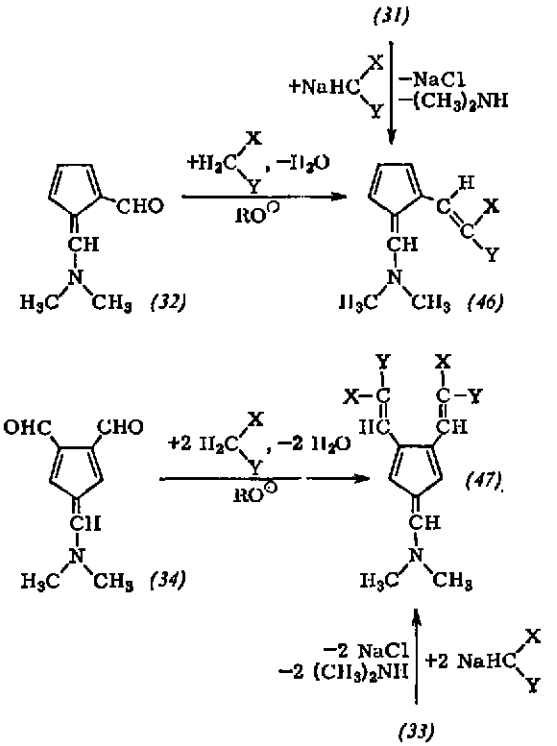
Correspondingly, on reaction with β-(*N*,*N*-dialkylamino)-acroleins and oxalyl chloride, compound *(27)*, where n = 1, yields the dark red fulvene-3,4-dipropenal *(44)*. The bis-immonium salts *(41)* and *(43)*, which are formed first, can be isolated as their perchlorates or iodides [35].



All of these new 6-dialkylaminofulvenaldehydes crystallize well. Their slight positive solvatochromism and the shift of their carbonyl stretching frequencies to lower values (1650 cm^{-1}; compared with aromatic aldehydes) suggest strong participation of the polar resonance



structures *(32b,c)*, *(34b,c)*, and *(35b,c)* in the ground state. With regard to their chemical properties, they only faintly resemble their isomeric aromatic aldehydes. They may otherwise be regarded as vinylogous amides.



Attempts to oxidize them to fulvenecarboxylic acids failed. Reduction of the dialdehyde *(34)* with lithium aluminum hydride leads to (*N*,*N*-dimethylaminomethyl) dimethylcyclopentadiene *(45)*, *i.e.*, as in the case of amides, both carbonyl groups are reduced directly to methyl groups. Subsequently, the exocyclic double bond is also reduced [29,33]. Aldehydes *(32)* and *(34)* behave similarly to *p*-dimethylaminobenzaldehyde toward compounds containing acidic CH groups. For example, in the presence of basic condensing agents, these aldehydes, and more especially, their immonium salts *(31)* and *(33)*, react with diethyl malonate, malonodinitrile, or other compounds containing active methylene groups, to yield fulvene derivatives of general formulae *(46)* or *(47)* [29,33,36]. The fulvenaldehyde *(34)* reacts with hydroxylamine, depending on the reaction conditions, to yield either the dioxime *(48)*, or, with simultaneous exchange of the dimethylamino group at carbon atom 6, the *N*-hydroxyaminofulvenedialdoxime *(49,a,b)*. Compounds *(32)* and *(34)* react similarly with hydrazine, thiosemicarbazide, and isonicotinic hydrazide. The dialdehyde *(34)* reacts with aliphatic and aromatic amines with simultaneous exchange of the dimethylamino group at carbon atom 6 to yield Schiff bases of general formulae *(50a,b)* and *(51a,b)* [92,33,37]. The infrared and NMR spectra of these compounds as well as energy considerations indicate large contributions from structures *(50b)* and *(51b)* [38].

6-Hydroxyfulvenaldehydes

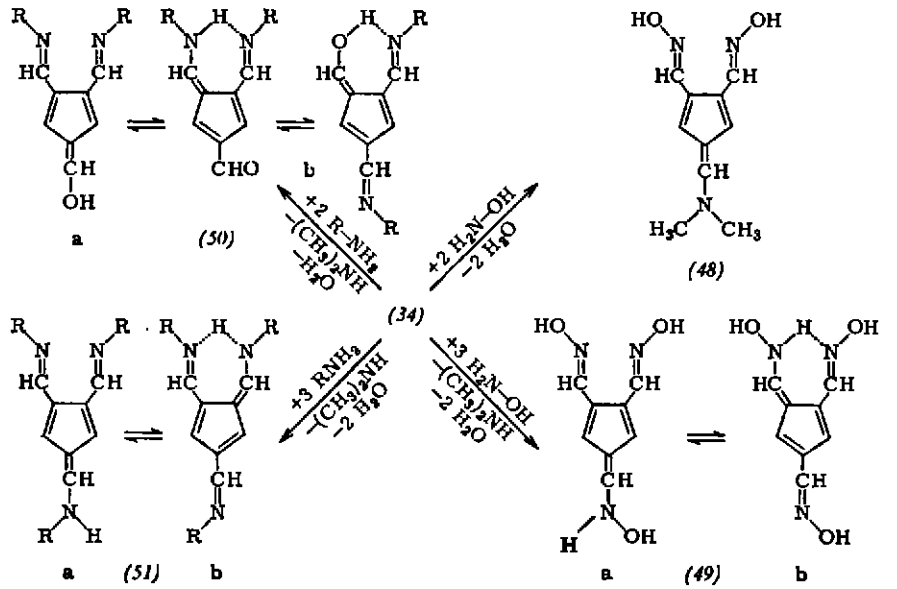
The mono- and dialdehydes *(32)* and *(34)* of 6-(*N*,*N*-dimethylamino)fulvene *(22)* react similarly to the latter with nucleophilic reagents undergoing replacement of

[36] *R. Oda, T. Shono*, and *K. Nishida*, J. chem. Soc. (Japan), *82* 1422 (1961).

[37] *C. König*, Ph. D. thesis, Universität Marburg, 1961.

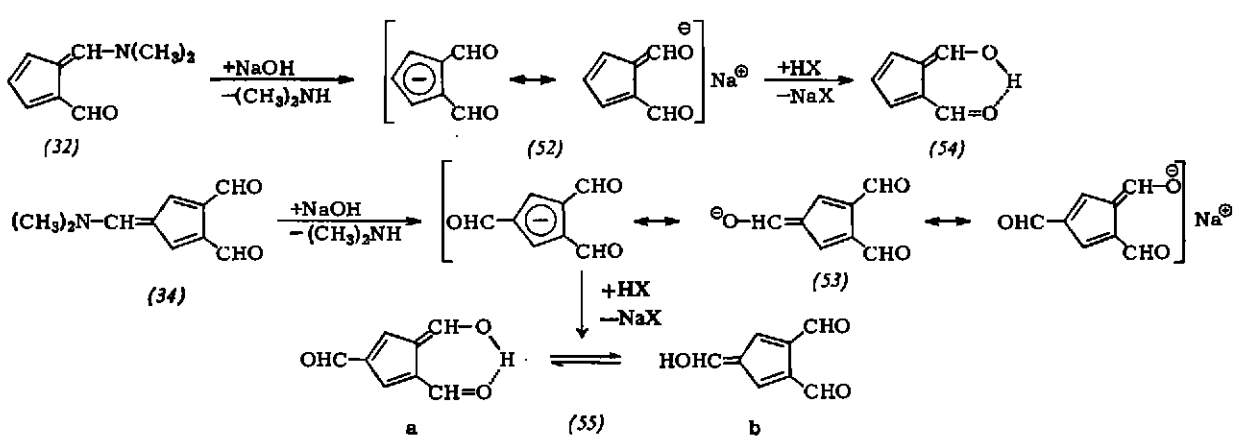
[38] *H. Musso, K. Hafner*, and *G. Ploß*, unpublished results.

the dimethylamino group. When treated with 2N sodium hydroxide, these fulvenealdehydes yield (slowly at 20 °C, rapidly when warmed) the water-soluble stable



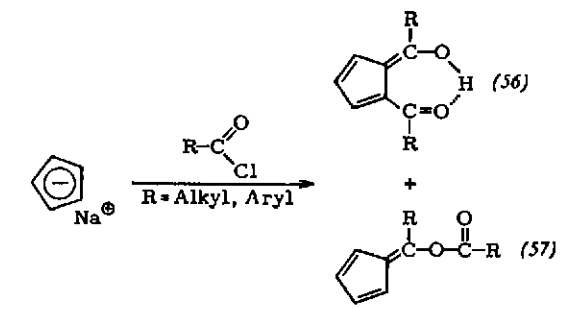
sodium salts of cyclopentadienedialdehyde and cyclopentadienetrialdehyde *(52)* and *(53)*, respectively. The latter are easily converted with dilute acids into the parent 6-hydroxyfulvenaldehydes *(54)* and *(55)*, which are also stable and crystallize well. Both of these hydroxymethylene compounds combine readily with amines to regenerate the corresponding 6-aminofulvenaldehydes [24, 29,33].

6-Hydroxyfulvene-2-aldehyde *(54)* and -2,4-dialdehyde *(55)* are readily volatile and strongly acidic. pK_a measurements give values of 1.8 ± 0.1 for the dialdehyde *(55)* and 4.5 ± 0.1 for the monoaldehyde. The cyclopentadiene derivatives are therefore equal in acidity to mineral acids or acetic acid [29,33]. Infrared and NMR spectroscopic investigations show that both compounds are



systems with almost completely symmetrical hydrogen bonds according to formulae *(54)* and *(55a)* [38]. Both fulvene derivatives have a pronounced tendency to form a π-electron sextet in the five-membered ring, which may contribute far more to the ground state resonance than the cross-conjugated fulvene structure, though the latter is certainly also involved. In their properties, the derivatives resemble the previously known 2-acyl-6-hydroxy-

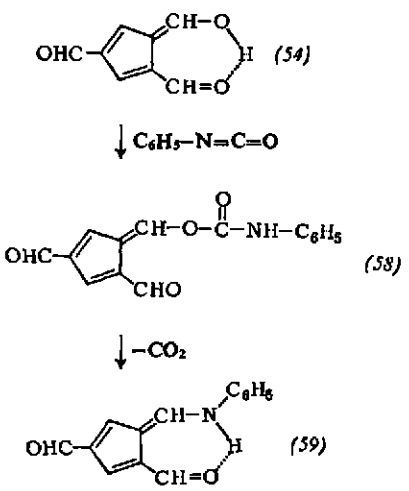
6-alkyl- and arylfulvenes of type *(56)* [39], which are formed, together with *o*-acyl derivatives of monoacylated cyclopentadienes *(57)*, on treating cyclopenta-



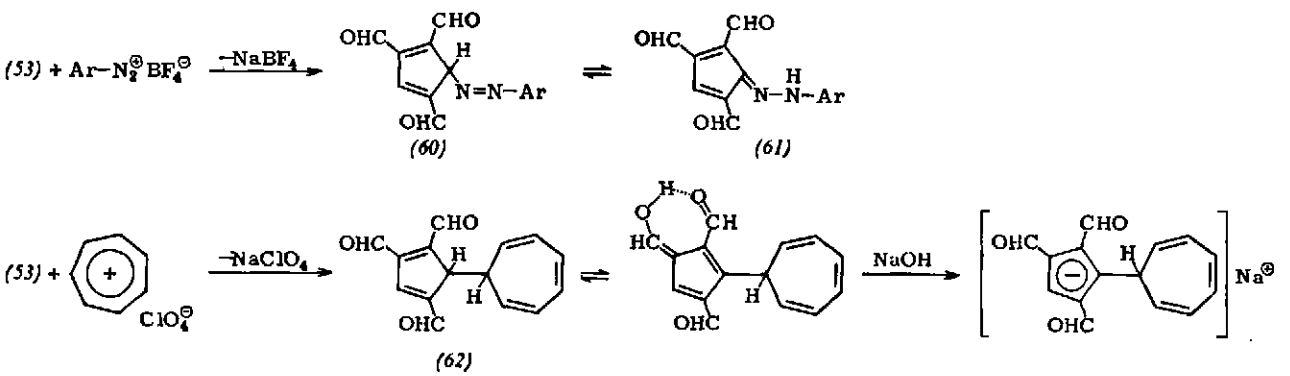
dienylsodium with acyl halides. Like compound *(56)*, the 6-hydroxyfulvenaldehydes give intensely green or red color reactions with ferric chloride. 6-Hydroxyfulvene-2-aldehyde *(54)* reacts with phenylisocyanate, as do other hydroxymethylene compounds, to give the *o*-carbanilide *(58)*, which is converted directly after its formation into 6-anilinofulvenedialdehyde *(59)* [29,33] with evolution of carbon dioxide. The fulvenedialdehyde

[39] *W. J. Hale*, J. Amer. chem. Soc. *34*, 1580 (1912); *38*, 2535 (1916); *W. J. Linn* and *W. H. Sharkey*, *ibid. 79*, 4970 (1957); *H. Dohm*, Ph. D. thesis, Universität Marburg, 1958; *R. Riemschneider* and *M. Krüger*, Mh. Chem. *90*, 573 (1959).

(55) undergoes substitution at the five-membered ring on treatment with electrophilic reagents. Thus, *(53)*



couples with diazonium salts to give a brownish-red compound, which, according to its infrared spectrum, is not the primary product *(60)* of the coupling but very



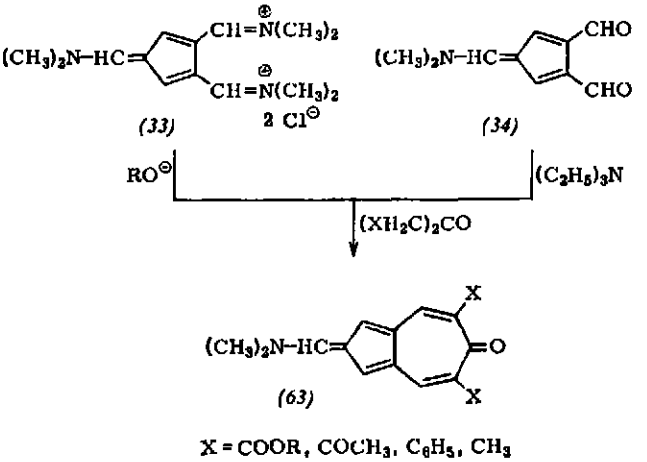
likely the tautomeric hydrazone *(61)* of 2,3,5-triformylcyclopentadienone. Alkylation of the sodium salt of triformylcyclopentadiene *(53)* also leads to fulvene derivatives which are substituted in the five-membered ring. Thus, 6-hydroxy-2-tropylfulvene-3,4-dialdehyde *(62)*, is formed in this way from tropylium perchlorate and easily affords a sodium salt; being a dihydrosesquifulvene derivative, *(62)* is of definite interest [29,33].

Syntheses of Bi- and Tricyclic Conjugated Ring Systems

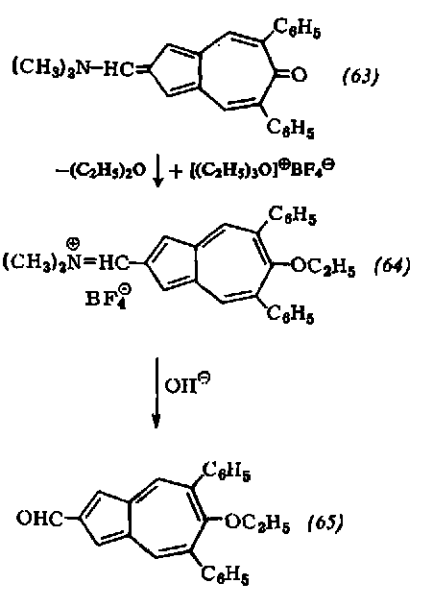
With suitable reagents, 6-aminofulvenealdehyde *(32)* and -dialdehyde *(34)*, as well as the corresponding hydroxy compounds, readily form new cyclic conjugated systems with fulvenoid structures.

Azulenes

6-(*N,N*-Dimethylamino)fulvene-3,4-dialdehyde *(34)*, which condenses with malonic acid derivatives or their immonium salts *(33)*, also condenses with diethyl acetonedicarboxylate, dibenzyl ketone, or diethyl ketone to give orange-red fulvenotropone derivatives of type *(63)*, which resemble quinone methides and which were previously inaccessible. Thus, for example, on alkylation with triethyloxonium fluoborate, the quinonoid azulene

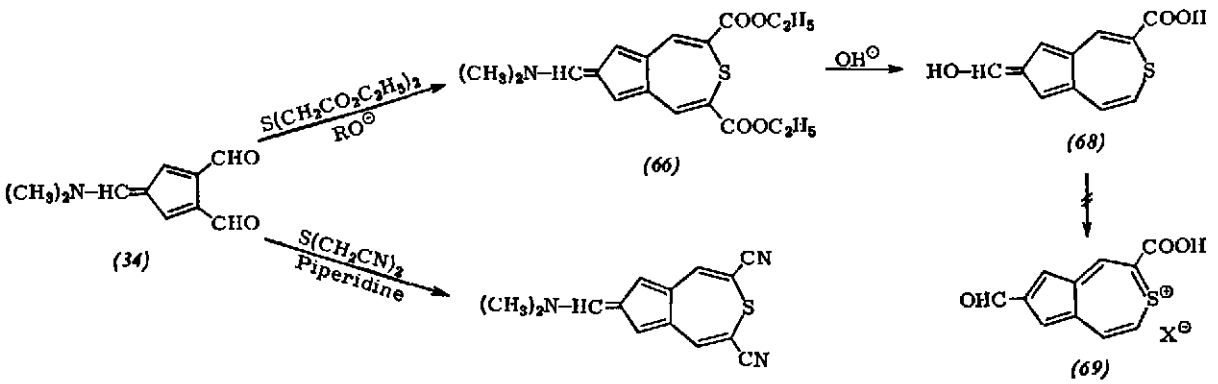


derivative *(63)*, where R = C_6H_5, is readily converted into the immonium salt *(64)*, which on alkaline hydrolysis gives a good yield of a blue compound, 5,7-diphenyl-6-ethoxyazulene-2-aldehyde *(65)*. The synthesis of this azulene derivative simultaneously confirms the structure of the preliminary step in the synthesis of the fulvenedialdehyde *(34)*, *viz.* the bis-aldimmonium salt *(33)* [24,29,37].



Thiepines

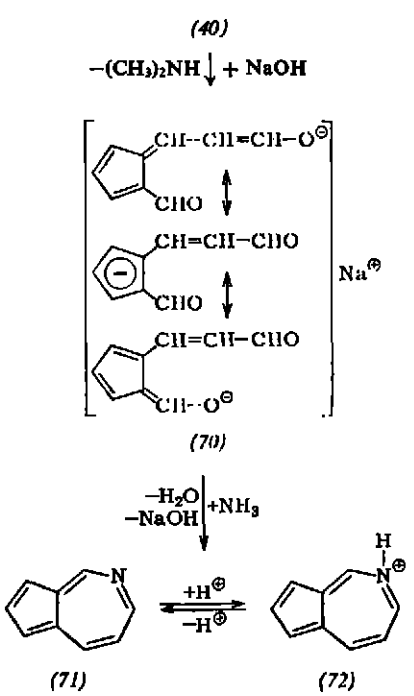
In the presence of alkaline condensing agents, the fulvenedialdehyde *(34)* reacts with diethyl thiodiglycolate or thiodiacetonitrile to yield systems with condensed five- and seven-membered rings, such as the red-brown



fulvenothipine derivatives *(66)* and *(67)*. Thus, a method has become available for the first time for the synthesis of thiepines condensed with a five-membered ring. On treatment with methanolic potassium hydroxide, compound *(66)* is converted by hydrolysis and decarboxylation into compound *(68)*, which so far has resisted all efforts to transform it into the cyclic conjugated sulfonium salt *(69)* [37], an isomer of the 1- or 2-thianaphthalenium ion [40].

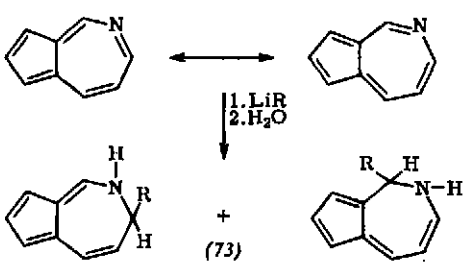
5-Aza-azulene

The hydroxyfulvene derivative *(70)* is easily accessible by treating 6-(*N*,*N*-dimethylamino)fulvene-2-prop-2'-en-1'-al *(40)* with sodium hydroxide and on treatment with aqueous ammonia, leads to new types of azulene derivatives. In this reaction, a 77% yield of the violet 5-aza-azulene *(71)* is obtained directly; this is the first representative of a bicyclic azulene with a hetero atom in the seven-membered ring and, being an azepine derivative, is of special interest. Chemically and physically, it resembles carbocyclic azulene and pyridine. Its ultraviolet and visible absorption spectrum resembles that of



azulene, especially in its fine structure, the absorption maxima being, however, hypsochromically shifted by 35 mμ; this corresponds to theoretical predictions by *H. Kuhn* [41]. On treatment with protons or alkylating agents, it is converted into the red azulene-immonium salt *(72)*, the protonation being reversed by bases. As expected, protonation or alkylation of the nitrogen – just as the presence of electronegative substituents at carbon atom 5 or carbon atom 7 of the azulene – effects a further hypsochromic shift of the absorption maxima [35,42].

As with pyridine, nucleophilic reagents add onto the carbon atoms adjacent to the nitrogen to yield the corresponding dihydro derivatives *(73)* [43].



Pseudo-azulenes

It has been known for a long time that, on replacement of a –CH=CH– group in cyclic conjugated systems by a hetero atom (sulfur, oxygen, NH group) possessing free electron pairs, the cyclic conjugation is more or less preserved. Thus, the heterocyclic systems *(74)* and *(75)* are closely related to electronically isosteric azulene derivatives. *Armit* and *Robinson* [3,44] as well as *Boyd* [45]

[40] *A. Lüttringhaus* and *N. Engelhard*, Chem. Ber. *93*, 1525 (1960).

[41] *H. Kuhn*, personal communication; see also *H. Kuhn*, Helv. chim. Acta *34*, 2371 (1951); Chimia *4*, 203 (1950); Fortschr. Chem. org. Naturstoffe (Wien) *16*, 169 (1958); *17*, 404 (1959).

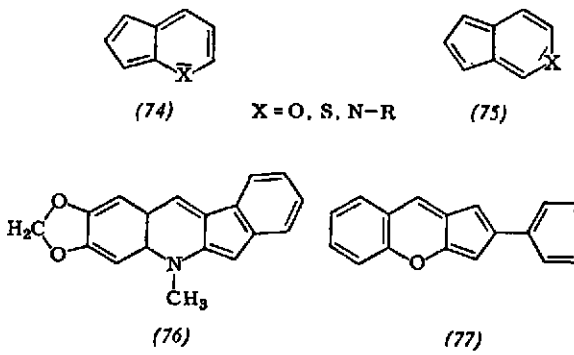
[42] *K. Hafner* and *M. Kreuder*, Angew. Chem. *73*, 657 (1961).

[43] *M. Kreuder*, unpublished results.

[44] *J. W. Armit* and *R. Robinson*, J. chem. Soc. (London) *121*, 827 (1922).

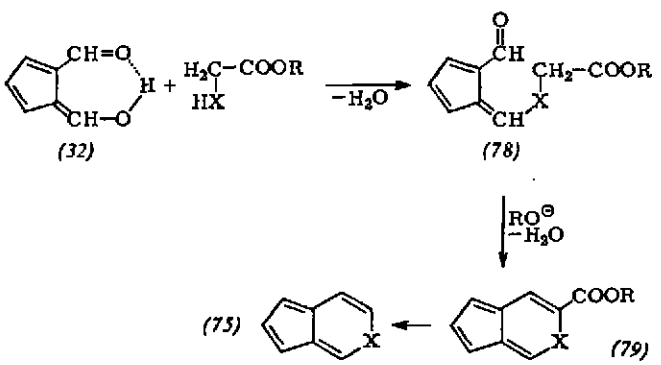
[45] *G. V. Boyd*, J. chem. Soc. (London) *1958*, 1978; *1959*, 55.

and *Treibs* and co-workers [46] have already prepared polycyclic compounds of type *(76)* and *(77)* that are



based on these pseudoazulenes. By dehydrogenation of the corresponding octahydro derivatives, *Anderson* et al. [47] and *R. Mayer* [48] recently obtained simple representatives of this class of compounds, such as the two isomeric cyclopentathiapyrans *(74)* and *(75)*, where X = S, and *N*-phenyl-2-pyridine *(75)*, where X = NC_6H_5.

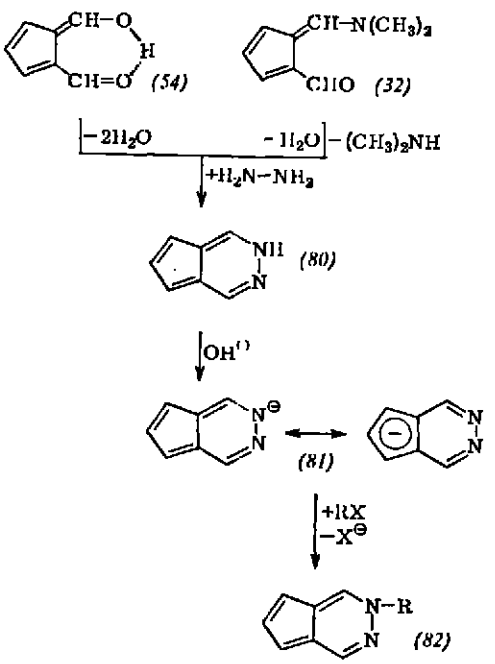
It is much simpler to prepare these pseudoazulenes by condensing 6-hydroxyfulvene-2-aldehyde *(32)* with the ethyl ester of sarcosine to give the aminofulvene *(78)*,



which, in the presence of basic condensing agents, subsequently undergoes intramolecular ring closure. A 76% yield of *(79)*, where X = NCH_3 and R = C_2H_5, is thus obtained.

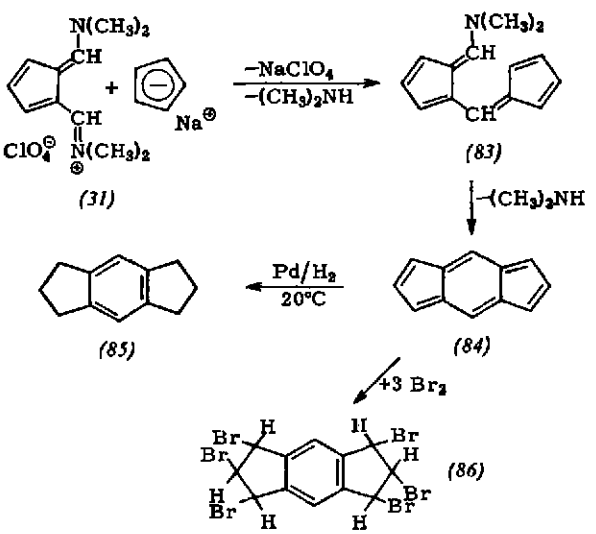
Dihydropyridazines

By another simple cyclic condensation, hydrazine reacts with 6-dimethylaminofulvene-2-aldehyde *(32)* or 6-hydroxyfulvene-2-aldehyde *(54)* to yield 2*H*-cyclopenta[*d*]pyridazine *(80)*, a compound previously unknown except in the form of its derivatives [39] and possessing a ring system isoelectronic with that of 5-azaazulene. With bases, this bicyclic system easily affords an anion *(81)*, which is stabilized by cyclic conjugation and can be isolated, for example, as its sodium salt. It reacts with alkylating agents to yield dihydropyridazine derivatives *(82)* which are alkylated at nitrogen atom 2 and which may also be obtained directly by the reaction of monosubstituted hydrazines and *(32)* or *(54)* [33].



s-Indacene

Using the aminofulvenaldehyde *(32)* as the starting material, a new member of the fulvene series of non-benzenoid cyclic conjugated systems, *viz. s*-indacene *(84)* [49], was prepared. Treatment of the aldimmonium perchlorate *(31)* with cyclopentadienylsodium in tetrahydrofuran at –40 °C yields 6-[6′-dimethylaminofulvene-2′-yl]fulvene *(83)* which undergoes rapid intramolecular ring closure, also below 0 °C, with elimination of an additional mole of dimethylamine. The hydro-



[46] *W. Treibs, W. Schroth, H. Lichtmann,* and *G. Fischer,* Liebigs Ann. Chem. *642*, 97 (1961); *W. Treibs* and *J. Beger, ibid. 652*, 192, 204, 212 (1962).

[47] *A. G. Anderson Jr., W. F. Harrison, R. G. Anderson,* and *A. G. Osborne,* J. Amer. chem. Soc. *81*, 1255 (1959); *A. G. Anderson Jr.* and *W. F. Harrison,* Tetrahedron Letters *1960*, No. 2, p. 11.

[48] *R. Mayer,* Angew. Chem. *69*, 481 (1957); *R. Mayer* and *U. Weise,* Naturwissenschaften *45*, 312 (1958).

[49] *E. Sturm,* diploma thesis, Universität München, in preparation; *R. D. Brown,* J. chem. Soc. (London) *1951*, 2391.

carbon is isolated as a red oil but has low thermal stability and is susceptible to autoxidation. On catalytic hydrogenation under mild conditions, it absorbs three moles of hydrogen to form the previously reported compound *s*-hydrindacene *(85)* [50]. Bromination of *s*-indacene to give hexabromo-*s*-hydrindacene *(86)* is also associated with a transition of the quinonoid system *(84)* to the energetically favored benzenoid system of *s*-hydrindacene *(85)*.

s-Indacene *(84)*, which is closely related to the still unreported compound pentalene [7], is a nonalternating hydrocarbon (like heptalen [51]) with twelve π-electrons. In agreement with theoretical considerations, *s*-indacene behaves more like a cyclopolyolefin than a nonbenzenoid "aromatic" system.

Conclusion

Discussions of "aromatic character" have resulted in recent years in fruitful theoretical proposals and in the synthesis of numerous nonbenzenoid cyclic conjugated systems. Despite systematic and critical attack from both the theoretical and experimental standpoint, the concept of "aromatic character" still remains to be precisely defined. The blurred boundary between distinctly olefinic and classical "aromatic" systems makes interpretation of the phenomenon difficult, and hard and fast divisions are meaningless. Nevertheless, the cyclic conjugation, electron delocalization energy, and chemical reactivity of any given compound have proved to be useful criteria for investigation of the relationships between its constitution and "aromatic character." This has been confirmed by the results reported in the present paper. By considering the fulvenes and several carbo- and heterocyclic systems derived from them as examples, the existence of some relationships between fine structure and chemical behavior in benzenoid and nonbenzoid compounds has been indicated. Furthermore, the great variety of reactivities of cross-conjugated systems has been demonstrated.

Sincere thanks are due to Prof. K. Ziegler, Prof. O. Bayer, the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft, Farbenfabriken Bayer, the Badische Anilin- und Soda-Fabrik, and Degussa for their generous support of our investigations.

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[50] *R. T. Arnold* and *E. Rondestvedt*, J. Amer. chem. Soc. 67, 1265 (1945).

[51] *H. J. Dauben* and *D. J. Bertelli*, J. Amer. chem. Soc. *83*, 4659 (1961).

Organic Derivatives of Mica-Type Layer-Silicates

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Dedicated to Prof. Dr. Ulrich Hofmann on the occasion of his 60th birthday

Mica-type layer-silicates such as montmorillonite and vermiculite are capable of exchanging their cations for other (including organic) cations, just like the zeolites. These derivatives swell in a variety of liquids. This paper presents a survey of the structures of organic derivatives of mica-type layer-silicates and illustrates some possibilities for their industrial utilization.

Introduction

One-dimensional intracrystalline swelling of the clay mineral montmorillonite was discovered just thirty years ago by *U. Hofmann, Endell,* and *Wilm* [1]. Since then, the phenomenon has been repeatedly reinvestigated [2]. This intensive research on montmorillonite is due primarily to its industrial utilization as a binder for molding sand, its uses in oil well drilling and in the production of catalysts, and its importance as a model substance in swelling studies [3]. In the past ten years, organic derivatives of montmorillonite have been developed and employed in the manufacture of thixotropic lacquers, thermostable lubricants, emulsion stabilizers, *etc.* [4].

In mica-type layer-silicates of composition represented by the limiting formulae

[1] *U. Hofmann, K. Endell,* and *D. Wilm*, Z. Kristallogr., Mineralog. Petrogr. Abt. A *86*, 340 (1933); Angew. Chem. *47*, 539 (1934).

[2] In this connection, see *K. Jasmund:* Die Tonminerale. 2nd Edit., Verlag Chemie, Weinheim 1955; *P. F. Kerr* and *P. K. Hamilton:* Reference Clay Minerals. Amer. Petrol. Inst. Research Project 49 (1949); *G. Brown:* The X-Ray Identification and Crystal Structures of Clay Minerals. Mineralogical Soc., London 1961; *R. C. Mackenzie:* The Differential Thermal Investigations on Clays. Mineralog. Soc., London 1957; *R. E. Grim:* Clay Mineralogy, McGraw-Hill, London 1953; *R. E. Grim:* Applied Clay Mineralogy. McGraw-Hill, London 1962; *M. Déribéré* and *A. Esme:* La Bentonite. 3rd Edit., Dunod, Paris 1952.

[3] *U. Hofmann*, Angew. Chem. *68*, 53 (1956).

[4] *O. P. Müller, J. W. Jordan,* and *J. J. Brancato*, Official Digest Federation Paint and Varnish Production Clubs No. *294*, 451 (1949); *E. P. Peterson* and *O. P. Muller*, US-Patent 2531825 (1950); *J. W. Jordan*, US-Patent 2531440 (1950); *E. A. Hauser*, US-Patent 2531427 (1950); *L. W. Carter, J. G. Hendricks,* and *D. S. Bolly*, US-Patent 2531396 (1950).

(a) $M_x^+ Y_{0-n} \left\{(Al^{3+}, Cr^{3+}, Fe^{3+}, Fe^{2+}, Mg^{2+}, Zn^{2+}, Ni^{2+})_{2-3}^{6+} (OH)_2 (Si_{4-x}Al_xO_{10})\right\}^{x-}$

and

(b) $M_x^+ Y_{0-n} \left\{(Al^{3+}, Cr^{3+}, Fe^{3+}, Fe^{2+}, Mg^{2+}, Zn^{2+}, Ni^{2+}, Li^{+})_{2-3}^{(6-x)+} (OH)_2 (Si_4O_{10})\right\}^{x-}$

zeolite-type cation exchange can occur, whereby the M^+ ions can be exchanged for other cations, including organic ones. With the exception of saturated hydrocarbons, any solvent molecules may be introduced as swelling agent Y. The quantity of swelling agent can be varied over a wide range. Since the quantity x of monovalent cations per $(Si, Al)_4O_{10}$ structural unit, *i.e.* the charge on the layer structure, may also vary, the result is an extraordinarily large variety of possible compounds; so far, about 9000 organic derivatives of montmorillonite have been prepared. The properties of these derivatives sometimes vary systematically in the sense of homologous series; at other times, unexpected properties appear.

Montmorillonite Derivatives with Exchangeable Inorganic Cations and Neutral Organic Molecules

Montmorillonite consists of two-dimensionally infinite macroanions electrostatically bonded by the cations located between them [1, 5, 6]. The energy required for swelling, *i.e.*, for increasing the distances between the layers by separation of the positive and negative charges, is provided by hydration or solvation of the cations and the anion layers. Since solvation energies are generally substantially lower than hydration energies, only molecules of substances that have high dielectric constants or the ability to form hydrogen bridges can be intercalated. The number of montmorillonite derivatives of this kind is therefore limited.

Intercalated neutral molecules can be exchanged by suspending the montmorillonite derivative in another liquid. Since no additional swelling is required for the exchange, and the distance between the layers sometimes even decreases, a series of further derivatives may be produced in this manner [7, 8].

Most of the bonds, with which these compounds are held in montmorillonite, are very weak. If an attempt is made to remove a constituent adhering to the surface, liquid also escapes from the interior of the crystal. Therefore, stoichiometric relationships are still not clearly established. Approximate values may be computed from the magnitude of the basal plane spacing if it is assumed that the difference between the density of the intercalated substance within the swollen compound and its density in the free state is negligible. This assumption is permissible when water is used as swelling agent. Here the maximum percentage deviation is only ±7% in the various stages of swelling of montmorillonite [9].

Glycol and glycerol are incorporated especially strongly [10]. Determination of the uptake of glycol or glycerol has proved to be a simple and reliable gravimetric method for determining the montmorillonite content of mixtures [11, 12]. Sugars are also strongly bonded, if Ca^{2+} or Sr^{2+} is present [13].

Normal solvated complexes with interplanar spacings of 15.9–19.4 Å are formed from sodium montmorillonite with anhydrous pyridine, α-picoline, or other aromatic nitrogenous bases [14]. In addition, water is absorbed in discrete stages from aqueous nitrogenous bases. There are two such hydrate stages in the case of pyridine, and as many as five in the case of α-picoline [15]; see Table 1.

Table 1. Basal plane spacing of Na-montmorillonite after intercalation of α-picoline and pyridine from anhydrous and aqueous solutions.

Water content of the suspension fluid [%]	Basal plane spacing [Å]	
	pyridine	α-picoline
0	19.4 and 14.8 [*]	15.9
2	diffuse [**]	21.9
5	diffuse [**]	21.9
10	23.3	diffuse [**]
15	23.3	25.7
20	23.3	27.9
25	diffuse [**]	27.9
30	diffuse [**]	diffuse [**]
35	diffuse [**]	
40	29.3	31.8
50	29.3	33.8

[*] On intercalation from a solution of pyridine in alkanes.

[**] „Diffuse" implies that the (00l) interferences are broadened and occur in irregular sequence, *i.e.* different interlayer spacings are mixed in a random manner.

Unexpected derivatives with neutral, colored chelate complexes are formed if the exchangeable cations between the silicate sheets react with organic components capable of forming complexes, *e.g.* Mg ions with quinalizarine, or Ni ions with diacetyldioxime [16]. In

[5] *C. E. Marshall*, Z. Kristallogr. Mineralog. Petrogr. Abt. A *91*, 433 (1935).

[6] *W. Noll*, Chem. d. Erde *10*, 129 (1936).

[7] *W. F. Bradley*, J. Amer. chem. Soc. *67*, 975 (1945); Amer. Mineralogist *30*, 704 (1945); Nature (London) *154*, 577 (1944); *157*, 159 (1946).

[8] *D. M. C. McEwan*, Nature (London) *154*, 577 (1944); *157*, 159 (1946); Trans. Farad. Soc. *44*, 349 (1948); *G. F. Walker*, Nature (London) *166*, 695 (1950); *G. W. Brindley* and *M. Ruston*, Amer. Mineralogist *43*, 627 (1958); *R. W. Hoffmann* and *G. W. Brindley*, Geochim. cosmochim. Acta (London) *20*, 15 (1960).

[9] *W. F. Bradley*, Nature (London) *183*, 1614 (1959); *R. C. Mackenzie*, *ibid. 183*, 1615 (1959); *181*, 334 (1958); *C. P. De Wit* and *P. L. Arens:* Trans. 4th Int. Congr. Soil Sci. Amsterdam 1959. Vol. 2, p. 59; *D. T. Oakes*, Clays and Clay Minerals 5, 46 (1958); *C. T. Deeds* and *H. v. Olphen*, Adv. Chem. Ser. *33*, 332 (1961).

[10] *W. F. Bradley*, *R. A. Rowland*, *E. J. Weiss*, and *C. E. Weaver*, Clays and Clay Minerals *5*, 348 (1958); *C. E. Weaver*, *ibid. 5*, 348 (1958).

[11] *R. S. Dyal* and *S. B. Hendricks*, Soil Sci. *69*, 421 (1950); *C.A. Bower* and *F. B. Gschwend*, Soil Sci. Amer. Proceed. *16*, 342 (1952); *P. J. S. Bryone*, Clays and Clay Minerals *2*, 241 (1954); *G. W. Kunze*, *ibid. 3*, 88 (1955).

[12] *E. B. Kinter* and *S. Diamond*, Clays and Clay Minerals *5*, 318, 334 (1958).

[13] *W. W. Emerson*, Nature (London) *186*, 573 (1960).

[14] *R. Greene-Kelley*, Trans. Farad. Soc. *51*, 412 (1955).

[15] *H. v. Olphen* and *C. T. Deeds*, Nature (London) *194*, 176 (1962); *R. Greene-Kelley*, Clay Min. Bull. *2*, 226 (1955); Nature (London) *184*, 181 (1959).

[16] *A. Weiss* and *U. Hofmann*, Z. Naturforsch. *6b*, 405 (1951).

this case, hydronium ions balance the negative charges of the silicate layers [17].

Montmorillonite with Intercalated Organic Cations

Onium ions such as ammonium, phosphonium, sulfonium, or oxonium ions may replace the inorganic cations [18–22]. This substitution occurs especially well with n-alkylammonium ions. The longer the n-alkyl chain, the steeper the exchange isotherm corresponding to increased bond strength [23]. Equilibrium is achieved after only a few hours for low-charged montmorillonites, but requires up to 14 months for highly charged material [24]. Surprisingly, with the latter, attainment of equilibrium takes less time with long-chain, *i.e.* larger ions than with short-chain ones; this behavior is consistent with the mechanism for change of lattice sites within the interior of the crystal.

The bonding strengths of the alkyl compounds decrease sharply in the series RNH_3^+, $R_2NH_2^+$, and R_3NH^+. Quaternary alkylammonium ions R_4N^+ behave quite differently: Asymmetrical ions, such as trimethylcetyl or dimethyl-di-n-octadecylammonium ions, must be classified among the primary ammonium ions, whereas symmetrical ions, on the other hand, rank behind the secondary ammonium ions. Because of the bulkiness of the groups, the bonding strengths of $R_2NH_2^+$, R_3NH^+, and symmetrical R_4N^+ also decrease rapidly with increasing charge of the montmorillonite layers. The behavior of sulfonium and oxonium ions is similar to that of R_3NH^+.

The exchange capacity for organic cations is, generally speaking, much the same as for small inorganic ions; this value is never exceeded [25]. An excess of alkylammonium salt can, of course, be taken up in place of the swelling agent, giving at times an appearance of higher exchange capacities. The exchange capacity is more limited in highly charged silicates, because here the organic cations can no longer be accommodated between the densely packed layers [26].

Intercalation of n-Alkylammonium Ions

On intercalation of n-alkylammonium ions, the resulting distance between the silicate layers depends upon the length of the alkyl chain and the layer charge. With increasing length of the alkyl chain, this distance increases alternately by a greater or lesser amount depending on whether the resulting number of carbon atoms in the intercalated chain is even or odd [25, 27]; see Figure 1. This means that the alkyl chains can be

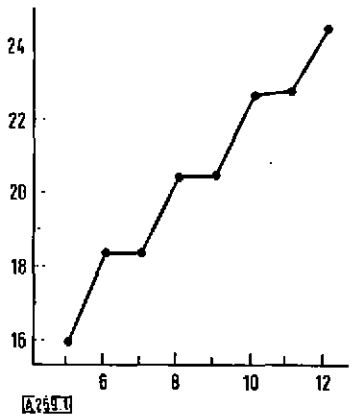

Fig. 1. Increasing basal plane spacings on intercalation of n-alkylammonium ions with increasingly long alkyl chains (batavite specimen from Kropfmühle near Passau, Germany); x in Formula (b) = 0.67.
Ordinate: basal plane spacing [Å]
Abscissa: number of carbon atoms in alkyl chain

present neither in the form of a statistical coil nor with their longitudinal axes parallel or perpendicular to the silicate layers.

If the alkyl chains were perpendicular (Fig. 2e), the interlayer distance would have to increase by approximately 1.26 Å per carbon atom. However, the average increase in Figure 1 is only 1.04 Å (= 1.26 Å·sin 56°). Thus, the true arrangement of the alkyl chains must correspond to the schematic representation shown in Fig. 2c or d. For reason of clarity, however, the planar *cis-trans*-configuration is shown in Fig. 2d which is less favored from the energy standpoint.

Figure 2 c or d clearly shows the pronounced stepwise changes in the interplanar distance encountered when the alkyl chain is lengthened. According to Figure 1, on passing from an odd to the next higher even number of carbon atoms, the interplanar distance increases by 2.0–2.1 Å, but on passing from an even to the next higher odd number, the increase is only 0.0–0.1 Å. The value of 2.0–2.1 Å/C atom exceeds the length of a single C–C bond (= 1.54 Å). The additional distance originates from the coordination of the terminal CH_3 group with the six-membered SiO ring. According to Figure 2c, one would expect the greatest variation in the interlayer distance to occur on transition from an even to an odd number of carbon atoms. The opposite is in fact observed because the terminal CH_3 group may dip into the six-membered SiO ring only when there is an even number of carbon atoms. On transition to an odd number of carbon atoms, the distance between the silicate layers must increase by the entire van der Waals radius of a CH_3 group.

The fact that CH_3 groups can penetrate far into the six-membered SiO ring has been shown in investigations of methylammonium montmorillonites by *Rowland* and *J. E. Weiss* [28]; here the basal plane spacing attained 12.5 Å. This value is some 3 Å greater than the thickness of the silicate layer and 2.0–2.5 Å greater than the basal spacing in NH_4 montmorillonite.

On replacing the methylammonium with the ethylammonium cation, the basal plane spacing becomes

[17] *A. Weiss*, Ph.D. Thesis, Technische Hochschule Darmstadt, 1953.

[18] *C. R. Smith*, J. Amer. chem. Soc. *56*, 1561 (1934); US-Patent 2033856 (1936).

[19] *S. B. Hendricks*, J. physic. Chem. *45*, 65 (1941).

[20] *H. Erbring* and *H. Lehmann*, Kolloid-Z. *107*, 201 (1944).

[20a] *R. E. Grim, H. W. Allaway*, and *F. L. Cuthbert*, J. Amer. ceram. Soc. *30*, 137 (1947).

[21] *E. A. Hauser* and *J. W. Jordan*, J. physic. Colloid Chem. *53*, 294 (1950).

[22] *J. W. Jordan*, Mineral. Mag. *28*, 598 (1949).

[23] *A. Weiss* and *E. Michel*, Z. anorg. allg. Chem. *296*, 313 (1958).

[24] *A. Weiss*, Z. anorg. allg. Chem. *297*, 258 (1958).

[25] *A. Weiss*, Clays and Clay Minerals *10*, in the press (1962).

[26] *A. Weiss*, Z. anorg. allg. Chem. *299*, 92 (1959); *A. Weiss* and *I. Kantner*, Z. Naturforsch. *16b*, 804 (1960).

[27] *A. Weiss, A. Mehler*, and *U. Hofmann*, Z. Naturforsch. *11b*, 341, 435 (1956).

[28] *R. A. Rowland* and *J. E. Weiss*, Clays and Clay Minerals *10*, (1962), in the press.

about 2.0 Å larger. If the alkyl chain is made even longer, the increase in the interplanar distance begins to depend also on the charge on the layer [29]. In

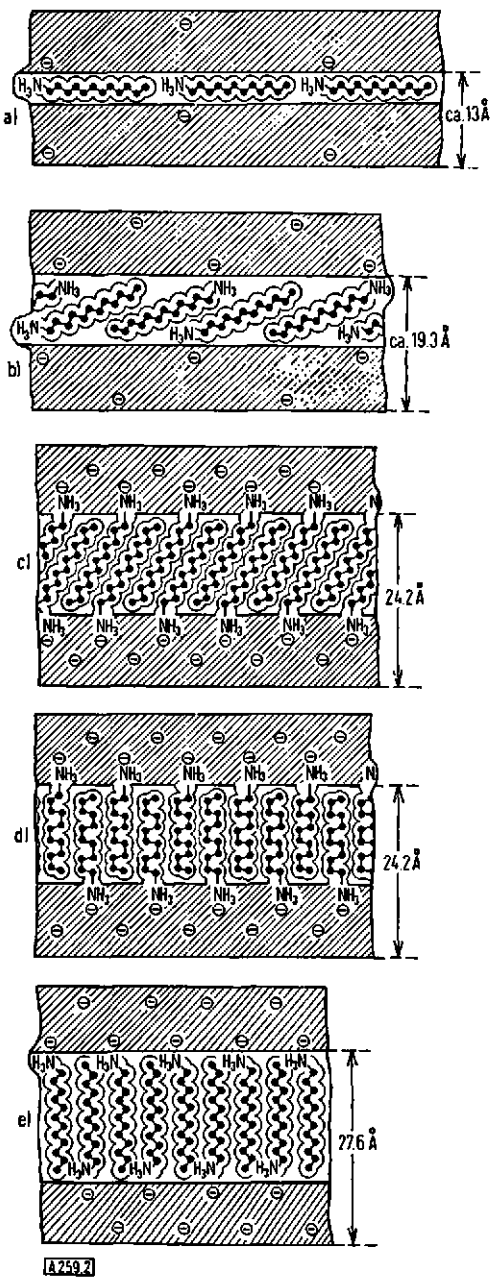

Fig. 2. Arrangements of alkylammonium ions in mica-type layer-silicates with different layer charges.

a) Very low charge
b) Medium charge.
c) Preferred arrangement with the formation of three hydrogen bonds per RNH_3^+ ion and with *trans,trans*-configuration.
d) As c) but with *cis,trans*-configuration (for reason of clarity the energetically unfavorable, planar *cis,trans*-configuration is shown here).
e) High charge.

Hatched areas: silicate layers.

highly charged silicate layers (x in Formula (b) *ca.* 1.0), the basal plane spacing increases, starting with the ethyl compound; if a somewhat lower charge density (x = 0.66) is present, it increases beginning with the n-butyl compound; with a still lower charge density (x = 0.33), it remains practically unchanged at 13–14 Å from the ethyl to the n-decylammonium derivative. The first increase is observed with the n-dodecylammonium compound. With an interlayer distance of 13–14 Å, there is a free space available, with a height of 4–5 Å; this is equal to the van der Waals diameter of the chain. Evidently, when the layer charge is low, the alkyl chains remain flat, until the layers are densely covered (Fig. 2a). As the charge density is increased, the chains begin increasingly to slip over one another (Fig. 2b) and stand more erect, until finally the arrangements in Fig. 2c or d are achieved. These arrangements are especially favored, because the hydrogen atoms of the RNH_3^+ group are able to form hydrogen bonds to the oxygen atoms of the six-membered SiO rings without distortion of their valence angle. A one-dimensional Fourier synthesis for an n-hexylammonium derivative yields N–H···O distances of 2.85 Å at the most, whereas for the NH_4^+ compound, it gives distances of 3.18 Å [30].

The relationship between length of the alkyl chain, basal plane spacing and charge density (Fig. 3) may be used to determine the charge on the layers of montmorillonoids [31]. Moreover, the montmorillonite may even be present in a mixture of other minerals. The distances between the silicate sheets may, of course, be affected by any preliminary treatment [25]. It is therefore necessary to carry out such work under standardized conditions.

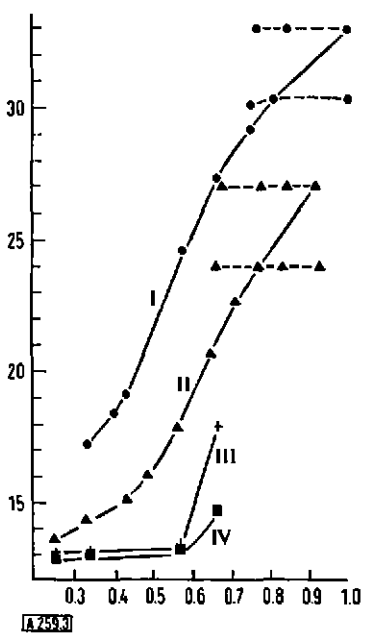

Fig. 3. Relationship of basal plane spacings to the charge on the layers in unswollen n-alkylammonium derivatives of mica-type layer-silicates:

Curve I: intercalation of n-$C_{18}H_{37}NH_3^+$
Curve II: intercalation of n-$C_{12}H_{25}NH_3^+$
Curve III: intercalation of n-$C_6H_{13}NH_3^+$
Curve IV: intercalation of n-$C_4H_9NH_3^+$

The dashed lines indicate basal plane spacings for unstable arrangements.

Ordinate: basal plane spacings [Å]
Abscissa: layer charge, = x in Formula (a) or (b)

Apart from its role in determining the exchange capacity of montmorillonoids, the value of the charge density has additional technological importance. Diffuse ionic double layers

[29] *A. Weiss*, Chem. Ber. *91*, 487 (1958); *A. Mehler*, Ph.D. Thesis, Technische Hochschule Darmstadt, 1956; *C. T. Cowan* and *D. White*, Trans Farad. Soc. *54*, 691 (1958).

[30] *A. Weiss*, *E. Michel*, and *A. Weiss* in: Hydrogen Bonding. Pergamon Press, London 1959, p. 495.

[31] *A. Weiss* and *I. Kantner*, Z. Naturforsch. *16b*, 804 (1960).

can be formed from monovalent inorganic ions only at charge densities below about 0.55. Under these conditions, the electrostatic repulsion of the diffuse ionic double layers takes the place of the electrostatic attraction between the cations and the silicate anions [32,33]. Thus, in water, swelling can progress until separation of the material into individual silicate sheets occurs.

Swelling of n-Alkylammonium Montmorillonites in Water and Electrolyte Solutions

With the exclusion of a few still unexplained exceptions [34], n-alkylammonium ions in montmorillonite do not build diffuse ionic double layers with water, since the alkyl groups are hydrophobic and the N–H···O hydrogen bridges with the silicate sheets are too strong. The swelling of n-alkylammonium montmorillonites in water is therefore completely different from that of unaltered montmorillonite. When the alkyl chains are short, no swelling takes place. Surprisingly, however, n-alkylammonium montmorillonites with longer alkyl chains do swell, although here stronger hydrophobism is actually to be expected. Figure 4 shows that a relationship exists between the charge density, the length of the alkyl chain, and the swelling in water.

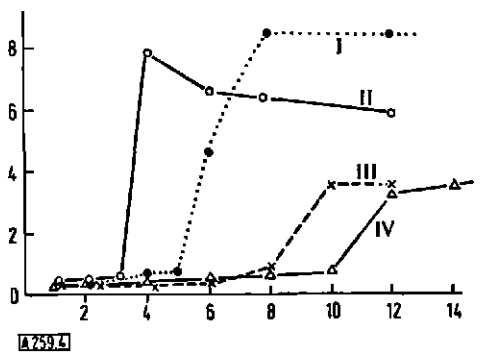

Fig. 4. Relationship between the length of the alkyl chain, the layer charge x, and the swelling power of n-alkylammonium montmorillonites in water:
Curve I: x in Formula (a) or (b) = 0.55
Curve II: x in Formula (a) or (b) = 0.66
Curve III: x in Formula (a) or (b) = 0.42
Curve IV: x in Formula (a) or (b) = 0.33
Ordinate: basal plane spacing in water [Å]
Abscissa: number of carbon atoms in the alkyl chain.

It is interesting that the samples become increasingly hydrophobic and organophilic to the same extent as their tendencies to intracrystalline swelling with water increase. Thus, when such samples are shaken with a toluene/water mixture, for example, montmorillonite derivatives with short alkyl chains are extracted into the aqueous phase, while the long-chain derivatives, which are capable of swelling in water, pass quantitatively into the toluene [35].

The swelling behavior in electrolyte solutions is also unexpected. If inorganic cations are intercalated between the silicate layers, the basal plane spacings are decreased when an electrolyte is added to the aqueous swelling agent [33]. The electrolyte limits the extension of the diffuse ionic double layers and correspondingly decreases the electrostatic repulsion. However, in the case of montmorillonite derivatives with long-chain n-alkylammonium ions, the interplanar distances increase when an electrolyte is dissolved in the swelling agent [25].

Swelling of n-Alkylammonium Montmorillonites in n-Alkyl Compounds

Swelling adopts a much simpler pattern in nonaqueous liquids than in water or aqueous electrolytes. In n-alkyl alcohols or n-alkylamines [25] of the same chain length as the intercalated n-alkylammonium ion, the charge density has no longer any effect on the interplanar distances (Table 2). No difference appears even in the number and sharpness of the (001) interferences.

Table 2. Basal plane spacing of n-alkylammonium derivatives of mica-type layer-silicates after swelling in n-alkyl alcohols or n-alkylamines with alkyl chains of equal lengths.

Mica-type layer-silicate	Intercalated: $n\text{-}C_6H_{13}NH_3^+$		$n\text{-}C_8H_{17}NH_3^+$		$n\text{-}C_{10}H_{21}NH_3^+$	
	Swelling agent: $n\text{-}C_6H_{13}OH$	Swelling agent: $n\text{-}C_6H_{13}NH_2$	Swelling agent: $n\text{-}C_8H_{17}OH$	Swelling agent: $n\text{-}C_8H_{17}NH_2$	Swelling agent: $n\text{-}C_{10}H_{21}OH$	Swelling agent: $n\text{-}C_{10}H_{21}NH_2$
from Hector, Calif., (USA)	25.5_3 Å	25.6_9 Å	30.1_1 Å	30.3_2 Å	37.4 Å	37.8 Å
Montmorillonite from Geisenheim (Germany)	26.0_1 Å	26.0_6 Å	29.9_1 Å	29.9_8 Å	36.9 Å	37.1 Å
Vermiculite from Kropfmühle (Germany)	25.4_9 Å	25.8_4 Å	30.3_2 Å	30.5_1 Å	37.1 Å	37.6 Å
Illite from Sarospatak (Hungary)	25.6_8 Å	25.9_4 Å	29.8_6 Å	29.9_6 Å	36.9 Å	37.2 Å
Muscovite from Norway	25.4_8 Å	25.6_2 Å	29.9_1 Å	29.9_3 Å	36.7 Å	36.9 Å
Biotite from Monroe, N.Y. (USA)	25.3_8 Å	25.6_3 Å	30.0_4 Å	30.2_4 Å	37.1 Å	37.3 Å

The similar behavior of the minerals montmorillonite, vermiculite, and the micas (Table 2) is due to the stoichiometry of the "clathrate" compounds (Table 3). The sum of the number of n-alkylammonium ions and the molecules

[32] *A. Weiss, G. Koch,* and *U. Hofmann,* Ber. dtsch. keram. Ges. *32,* 12 (1955).

[33] *A. Weiss,* Chem. Ber. *91,* 487 (1958).

[34] *G. F. Walker,* Nature (London) *187,* 312 (1960); *W. G. Garrett* and *G. F. Walker,* Clays and Clay Minerals *9,* (1962), in the press.

[35] *A. Weiss,* Angew. Chem. *73,* 549 (1961).

Table 3. Molar ratio $[RNH_3^+]$: [Y] per $(Si, Al)_4O_{10}$ unit in swollen n-alkylammonium derivatives of mica-type layer-silicates.

Swelling agent Y	Hectorite from Hector, Calif. (USA)	Montmorillonite from Gelsenheim (Germany)	Montmorillonite from Cyprus	Beidellite from Unterrupsroth (Germany)	Saponite from Groschlattengrün (Germany)	Batavite from Kropfmühle (Germany)	Muscovite from Norway
$n\text{-}C_4H_9OH$ to $n\text{-}C_{18}H_{37}OH$	0.25 / 1.75(1.82)	0.33 / 1.67(1.74)	0.40 / 1.60(1.66	0.58 / 1.42(1.50)	0.57 / 1.43(1.50)	0.67 / 1.33(1.40)	0.92 / 1.08(1.10)
$n\text{-}C_4H_9NH_2$ to $n\text{-}C_{18}H_{37}NH_2$	0.25 / 1.75(1.82)	0.33 / 1.67(1.75)	0.40 / 1.60(1.68)	0.58 / 1.42(1.48)	0.57 / 1.43(1.47)	0.67 / 1.33(1.39)	0.92 / 1.08(1.13)
$n\text{-}C_3H_7CHO$ to $n\text{-}C_{17}H_{35}CHO$	0.25 / 1.75(1.77)	0.33 / 1.66(1.69)	0.40 / 1.60(1.63)	0.58 / 1.42(1.45	0.57 / 1.43(1.46)	0.67 / 1.33(1.35)	0.92 / 1.08(1.10)
$n\text{-}C_3H_7COOH$ to $n\text{-}C_{17}H_{35}COOH$	0.25 / ca. 1.75	0.33 / ca. 1.66	0.40 / ca. 1.60	0.58 / ca. 1.42	0.57 / ca. 1.43	0.67 / ca. 1.33	0.92 / ca. 1.08

Y = molecule of swelling agent. Values in parentheses are maximal values.

of swelling liquid per $(Si, Al)_4O_{10}$ unit is nearly the same in all mica-type silicates, and amounts to 2.00–2.07, if compounds with unbranched alkyl chains are used as swelling agents. This number is largely independent of the nature of the functional groups, as the results of experiments with alcohols, amines, aldehydes, nitriles, carboxamides, and carboxylic acids have shown. Additional neutral molecules evidently fill the vacant cation positions in low-charged montmorillonites.

In all of these "clathrate" compounds, the alkylammonium ions and the molecules of swelling fluid are arranged in a bimolecular layer between the silicate anions (Fig. 5).

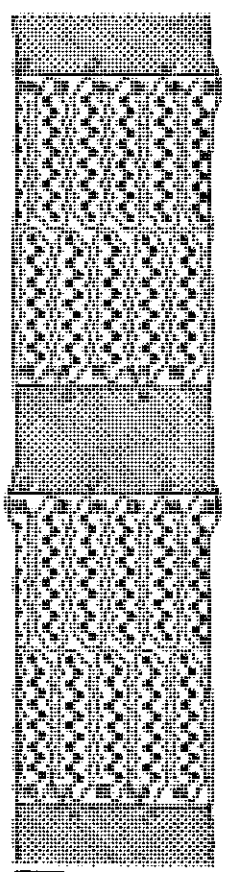

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Fig. 5. Arrangement of n-alkylammonium ions and of n-alkyl compounds intercalated as swelling agents between silicate layers (hatched areas). The total (n-alkylammoniumions plus molecules of n-alkyl compound) = 2.00 to 2.07 per $(Si, Al)_4O_{10}$ unit. Here, an n-alkyl alcohol is drawn as an example of a swelling agent.

Since only about 23 Å² of surface area are available for each $(Si, Al)_4O_{10}$ unit, and since a fully extended n-alkyl chain in crystalline compounds requires 18–21 Å², the alkyl chains must be very densely packed here, with their longitudinal axes perpendicular to the silicate layer; this is confirmed by the basal plane spacings measured [25].

These results are consistent with the fact that when the molar ratio of n-alkylammonium ions to n-alkyl alcohol is 1.0, the basal spacing is determined only by the sum of the carbon atoms in the alkyl chains of the cation and the alcohol. The same is observed with uranyl compounds which are capable of swelling, *e.g.* $M^+(UO_2PO_4)$, $M^+(UO_2AsO_4)$, and $M^+(UO_2VO_4)$ [36].

The maximum intercalatable quantity is most readily determined by means of thermogravimetric analysis. If the samples are triturated in the course of the thermal analysis, a

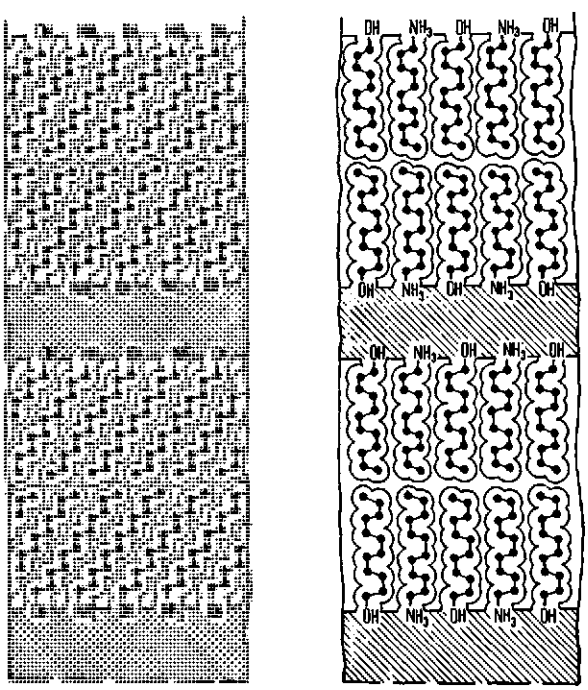

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Fig. 6. Possible metastable arrangements of n-alkylammonium ions and of molecules of n-alkyl compounds (the swelling agent), bound between silicate layers (hatched areas). The total (n-alkylammonium ions plus molecules of n-alkyl compound) = 1.60 to 1.75 per $(Si, Al)_4O_{10}$ unit.

[36] *A. Weiss, K. Hartl,* and *U. Hofmann,* Z. Naturforsch. *12b,* 351 (1957).

metastable intermediate stage can be obtained in which the sum of the n-alkylammonium ions and the neutral n-alkyl compounds per $(Si, Al)_4O_{10}$ unit lies between 1.6_0 and 1.7_5. In this case, the sheet separation (*i.e.* basal plane spacing minus the thickness of the silicate anion) is smaller by a factor of sin 56° than in the most highly swollen samples. This may be explained by the arrangement of the alkyl chains shown in Fig. 6.

Swelling of n-Alkylammonium Montmorillonites in Hydrocarbons

Saturated hydrocarbons cannot be intercalated into n-alkylammonium montmorillonites. On the other hand, alkenes and aromatic hydrocarbons are absorbed vigorously, even when present at very high dilution in saturated hydrocarbons. The resulting basal plane spacings are, however, not readily explainable in all cases. The aromatic rings arrange themselves parallel to the silicate layers, insofar as the steric conditions permit.

Swelling of n-Alkylammonium Montmorillonites in Compounds with Branched Alkyl Chains

With regard to swelling in compounds containing branched alkyl chains, such as ethers, esters, ketones, and similar compounds, the relationships are especially unclear. Besides the size and the form of the intercalated molecules, the position of the polar group also plays a role in their orientation within the interior of the crystal. The polar group is almost always in a position in direct contact with the silicate layer, so that the arrangements formed have various packing densities, depending on the molecular shape. Thus, stoichiometric relationships cannot be estimated simply by calculation from the volume of the free molecules. It is especially perplexing that, owing to their effect on the hydrogen bonds, molecules with strongly negative groups cause the preferably prone alkyl chains of n-alkylammonium cations to stand erect and thereby cause sheet separation that has no direct relationship to their dimensions.

From aqueous solutions polar organic compounds are preferably incorporated. Alkylammonium montmorillonites might therefore conceivably be used for waste-water purification. *Cowan* [37] has reported on quantitative experiments on the removal of phenols.

[37] *C. T. Cowan*, Clays and Clay Minerals *10* (1962), in the press.

Di- and Trialkylammonium Montmorillonites

Montmorillonites with unsymmetrical cations, such as methyl-n-dodecylammonium, hydroxyethyl-n-decylammonium, or di-(hydroxyethyl)-n-decylammonium, have properties similar to those of the n-alkylammonium montmorillonites. With large, symmetrical di- and trialkylammonium ions, however, the situation is quite complicated even in unswollen samples because, as a result of the bulky structure of these cations, cavities open to the exterior are formed in the montmorillonite. These cavities can be filled with gases or liquids of small molecular size, as occurs in molecular sieves, with no apparent change in the lattice dimensions.

Montmorillonites with Quaternary Alkylammonium Ions

No peculiarities appear on intercalation of small quaternary alkylammonium ions. The products swell only slightly in water and in most nonaqueous liquids [38]. Gases can be absorbed in a zeolite-type exchange, with no change in the basal plane spacings [39].

Materials of this kind are therefore suited for special gas-chromatographic separations [40].

Because of their colloidal chemical properties, derivatives with unsymmetrical ions, such as trimethyl-n-hexadecylammonium or dimethyldi-n-octadecylammonium ions, are of special importance. These derivatives are the chief constituents of the commercial Bentones C 34 and C 38®. These montmorillonites form thixotropic gels with high contents of liquid with the majority of slightly polar liquids, excluding saturated hydrocarbons (Table 4) [41].

Table 4. Volumes of thixotropic gels of alkylammonium montmorillonite in various fluids.

Suspension fluid	Volume of thixotropic gels requiring 6 seconds for gelation (ml liquid/3 g of montmorillonite)				
	$[n\text{-}C_{12}H_{25}NH_3]^+$-derivative	$[n\text{-}C_{18}H_{37}NH_3]^+$-derivative	$[n\text{-}C_{16}H_{33}N(CH_3)_3]^+$-derivative	$[(n\text{-}C_{18}H_{37})_2N(CH_3)_2]^+$-derivative	$[n\text{-}C_{16}H_{33}N$⟨⟩$]^+$-derivative
methanol	17.7	12.9	18.0	8.1	11.7
acetone	15.6	12.0	23.1	21.6	20.1
ethyl methyl ketone	19.8	18.0	16.5	29.4	23.1
cyclohexanone	17.7	12.3	32.4	24.0	27.0
diethyl ether	27.0	23.6	35.7	43.5	12.9
toluene	15.6	18.3	46.5	41.7	29.7
nitrobenzene	39.3	34.5	92.4	>120	89.1

Even very limited additions of these raise the viscosity of toluene and other solvents considerably (Fig. 7) [42].

[38] *A. Weiss*, Z. anorg. allg. Chem. *299*, 92 (1959).

[39] *R. M. Barrer* and *D. M. McLeod*, Trans. Farad. Soc. *50*, 980 (1954); *R. M. Barrer* and *J. S. S. Reay*, *ibid. 53*, 1253 (1957).

[40] *D. White*, Nature (London) *179*, 1075 (1957).

[41] *J. W. Jordan*, J. physic. Colloid. Chem. *53*, 294 (1950); *J. W. Jordan*, *B. J. Hook*, and *C. M. Finlayson*, *ibid. 54*, 1196 (1950); *A. Mehler*, Ph.D. Thesis, Technische Hochschule Darmstadt, 1956; *W. Immel*, Ph.D. Thesis, Technische Hochschule Darmstadt, 1960.

[42] *J. W. Jordan* and *F. J. Williams*, Kolloid-Z. *137*, 40 (1954).

This property has led to the utilization of montmorillonites with quaternary alkylammonium ions in the production of thixotropic lacquers and thermostable lubricants. In mixtures containing mainly polar liquids,

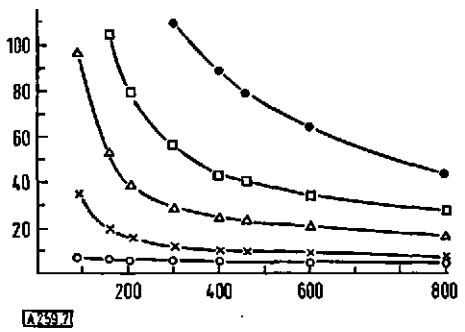

Fig. 7. Relationship between the viscosity of some suspensions of dimethyldi-n-octadecylammonium montmorillonite in toluene and the rotation speed of the rotor in a Stormer viscosimeter.

o–o–o 5% solid
x–x–x 6% solid
Δ–Δ–Δ 7% solid
□–□–□ 8% solid
●–●–● 9% solid

Ordinate: viscosity [cp]
Abscissa: rotation speed [rpm]

n-octadecylammonium montmorillonites (®Bentone C 18) are preferred. The intensive gel formation of these onium montmorillonites is always associated with the presence of traces of water [43]. The water molecules evidently interlink the platelike montmorillonite crystals by hydrogen bridges to form wide-mesh frameworks (edge-to-edge linkage) [44].

Montmorillonites with Alkylene-α,ω-diammonium Ions

The swelling properties of mica-type layer-silicates loaded with alkylene-α,ω-diammonium ions depend largely upon the number of carbon atoms in the alkylene chain. If this number is even, the two NH_3^+ groups are in direct contact with both the adjacent anion layers. With a *cis-trans* chain that is helical or inclined at 56°, all six *N*-hydrogen atoms can form hydrogen bonds (Fig. 8a) [45]. The basal plane spacing that corresponds to this arrangement should therefore provide an upper limit to the swelling, since at least two hydrogen bridges per ion must be broken in order to exceed this distance [33].

If the alkylene chain contains an odd number of carbon atoms, further swelling will cease when the extended chains stand perpendicular to the anion sheets (Fig. 8b). Further swelling would require separation of the positive and negative charges.

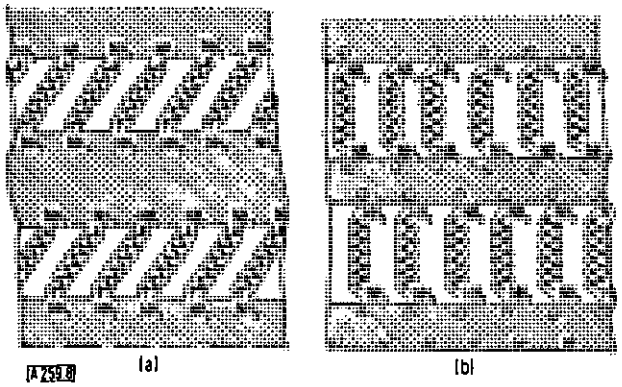

Fig. 8. Arrangement of alkylene-α,ω-diammonium ions in the most highly swollen state of mica-type silicates.

a) Alkylene chains with even numbers of carbon atoms.
b) Alkylene chains with odd numbers of carbon atoms.

Hatched areas: silicate sheets.

Although the basal plane spacing in the most highly swollen state is independent of the charge density, in the dry state, it is strongly influenced by the charge. When the charge density is low, the chains lie flat; when it is higher, they are coiled into a correspondingly denser packing. In the swelling process, the volume of the swelling agent intercalated is independent of its nature, being constant for any given charge density of the silicate layers. As the charge density increases, there is an increasingly greater limitation on the shape and size of the molecules: the alkylene chains spread the sheets apart like rigid columns. The higher the charge density, the more closely these columns are packed together and the more limited is the space which the swelling fluid can occupy (Table 5).

Table 5. Calculated and observed basal plane spacings of batavite with intercalated alkylene-α,ω-diammonium ions.

Cation $^+H_3N-(CH_2)x-NH_3^+$	Basal plane spacings [Å] dried at 60 °C and 0.1 mm Hg	under maximum swelling	calculated for the arrangements in: Fig. 8a	Fig. 8b
x = 0	10.0	10.0	11.5	
2	12.3	12.6	12.9	
4	12.9	15.1	15.0	
6	15.8	17.3	17.1	
8	17.7	19.4	19.1	
10	17.2	21.5	21.2	
12	17.6	23.8	23.3	
3	12.3	12.8		15.0
5	12.8	17.4		17.9
7	13.9	20.0		20.4
9	17.1	21.8		22.9
11	17.4	25.4		25.4

Intercalation of Alkaloid Cations

Alkaloid cations are very strongly bound by mica-type layer-silicates [46]. Thus, they are absorbed from even very dilute solutions. When there is enough excess montmorillonite, *i.e.* as long as the alkaloid cations remain loosely packed within the montmorillonite, the equilibrium concentration of many alkaloids in the

[43] *V. R. Damerell* and *E. Milberger*, Nature (London) *178*, 200 (1956); *A. Weiss* and *W. Immel* in *U. Hofmann:* Internat. Kongr. für grenzflächenaktive Stoffe. Mainzer Universitäts-Druckerei, Vol. II B, p. 669.

[44] *A. Weiss*, Acta Rheolog., in the press.

[45] *A. Weiss* and *E. Michel*, Z. anorg. allg. Chem. *306*, 278 (1960).

[46] *A. Weiss, I. Koch, G. Göring*, and *A. Schreiber*, unpublished results.

solution falls below the limit of detectability. However, quantitative cation exchange is possible only when the sheet charge is low.

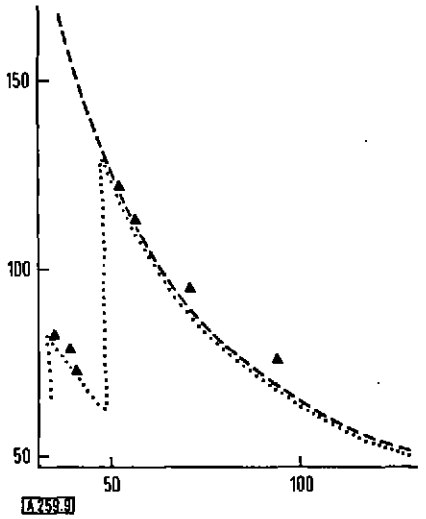

Fig. 9. Relationship between the cation exchanger capacity and the magnitude of the equivalent surface area in mica-type layer-silicates.
— — — Calculated exchange capacity without steric hindrance.
..... Calculated exchange capacity for a cation with an area of 50 Å².
▲ Exchange capacity determined for codeine cations.
Ordinate: quantity of exchangeable cations (meq./100 g)
Abscissa: equivalent surface area (Å²/unit charge).

Figure 9 summarizes the calculated and the observed relationships between the exchange capacity and the charge density. Here the equivalent surface area (Å²/unit charge) replaces the charge density in equivalents per $(Si, Al)_4O_{10}$ unit. This value indicates the surface area on the anion layer available for one monovalent cation [33]. In the absence of steric hindrance, the exchange capacity should increase hyperbolically as the equivalent surface diminishes. If, however, the value of the equivalent surface area drops below the surface area required by the exchangeable cation, the final exchange capacity must decrease, unless an arrangement in a bimolecular layer is possible. Since, at the same time, the basal plane spacing and hence the third dimension of the exchanged cation can also be determined, the shape of large cations that are not easily deformed can be ascertained in this fashion. This method yields good results for codeine (area occupied per molecule = 46–50 Å², thickness = 8.1–8.6 Å, molar volume = 373 to 430 Å³, molar volume calculated from molecular weight and density = 377 Å³) [46].

The intracrystalline swelling capacity is largely blocked by alkaloid cations. With nicotine, however, the intercalation compound still swells in water. On the other hand, zeolitic uptake of liquid is always possible whenever closest packing of the cations does not occur.

Intercalation of Amino Acids and Proteins

Amino Acids, peptides, and proteins can also be intercalated into mica-type layer-silicates [47]. At low pH values, proteins are exchanged almost quantitatively. With increasing pH values, the number of cationic positions in the protein drops, and the exchange becomes incomplete [48]. The reaction with protamines proceeds especially readily (Table 6). Here the swelling capacity is probably determined largely by the guanido groups; the formation of hydrogen bridges from these to the silicate sheets is promoted by the symmetry relationships. This is also indicated by investigations with pure guanidine and aminoguanidine montmorillonites [49]. Albumins, globulins, and prolamines are also intercalated. With serum globulins, the protein seems to penetrate the lattice to only about 20–30 Å from the outer edge of the silicate crystal. Albumins spread out between the silicate layers. The basal plane spacing of 14.5–15.0 Å makes it clear that, at the most, a sheet thickness of 5.5–6.0 Å is available for the extended protein [16, 50]. Gelatine can be bound in two arrangements, with basal spacings of about 15 Å and about

Table 6. Cation exchange in mica-type layer-silicates with proteins (salmine from herring sperm)

Mica-type layer-silicate	Equivalent surface area of silicate ion [Å²/unit charge]	pH during exchange		Amount of bonded protein [mg/g of layer-silicate]		Basal plane spacing of reaction product [Å]	
		initial value	final value	calculated	determined	dry	in H_2O
Montmorillonite from Geisenheim (Germany)	75	2.5	2.7	218	222	14.8	17.1
		4.6	5.9	218	248	15.7	17.7
		8.7	8.0	218	262	15.9	18.0
		11.2	8.5	252	267	16.9	18.4
		12.1	11.4	488	266	16.9	18.3
Nontronite from Grube Ficht (Germany)	60	2.5	2.7	263	258	15.3	18.0
		4.6	3.9	263	250	15.9	19.0
		8.7	7.2	263	250	16.1	18.9
		11.2	7.7	303	272	17.5	19.3
		12.1	11.4	588	285	17.5	20.3
Beidellite from Unterrupsroth (Germany)	57	2.5	2.7	316	263	15.5	18.8
		4.6	5.4	316	258	17.0	19.8
		8.7	8.3	316	289	17.3	20.1
		11.2	10.0	363	283	17.3	20.1
		12.1	11.9	706	386	17.3	20.2

[47] *L. E. Ensminger* and *J. E. Gieseking*, Soil Science *48*, 467 (1939); *51*, 125 (1941); *53*, 205 (1942); *A. Weiss* and *U. Hofmann*, Z. Naturforsch. *6b*, 405 (1951).

[48] *A. Weiss* and *G. Koch*, Ph.D. Thesis, Technische Hochschule Darmstadt, 1960.

[49] *C. W. Beck* and *G. Brunton*, Clays and Clay Minerals *8*, 22 (1960).

[50] *O. Talibudeen*, Trans. Farad. Soc. *51*, 582 (1955).

18 Å, respectively [51]. Tobacco mosaic virus is not taken up by layer-silicates [52].

Neutral or basic amino acids are bound as cations [16]. In the weakly acid or neutral pH range, they may also be intercalated as neutral molecules replacing the swelling agent, if inorganic cations are bound at the same time [53, 54]. Both variants differ in interlayer distances, quantity of amino acids bound, and swelling in water. Amino acids intercalated as neutral molecules are displaced by large quantities of water.

Organic Derivatives of Mica-Type Layer-Silicates in Petroleum Deposits and their Surroundings

Mica-type layer-silicates with unusual basal plane spacings containing organic compounds occur in petroleum deposits and their surroundings [55]. The oil in oil shales appears to be stored deep within the interior of montmorillonite minerals [56]. It is conjectured that such montmorillonite minerals have played an essential part in the genesis of petroleum deposits [57]. Perhaps this part was limited to the storage or transport of petroleum. However, it may have been in direct connection with petroleum formation, since mixtures of aliphatic, cyclic, and aromatic hydrocarbons are formed when oxygen is excluded during thermal decomposition of organic derivatives of montmorillonite minerals [58]. The high nitrogen contents of such mica-type layer-silicates in the vicinity of petroleum deposits explains the hitherto baffling deficit in the elemental balance. This nitrogen is partly bound in putrescine and cadaverine montmorillonites, which are also found in nearly pure form [59].

Montmorillonite Derivatives with Si–C– and Si–O–C-Bonds

For the sake of completeness, some mention should also be made of the work performed by *Deuel* and his colleagues [60] on montmorillonite derivatives with Si–C and Si–O–C bonds. The hypothesis that a cation exchange capacity corresponding to the quantity of reactive Si–OH groups exists in the H-form of montmorillonite could not be confirmed [61,62]. Only the Si–OH groups lying at the edge of the prism faces can react. Their number is limited and depends on the diameter of the montmorillonite crystal [24]. Since the predominant part of the surface of the platelike montmorillonite crystals is made up by basal planes, changes in the surface properties such as occur with SiO_2 are not observed [63].

Catalytic Reactions in Mica-Type Layer-Silicates

Chemical reactions occur in the layers between the silicate anions that do not take place under similar conditions in free solutions. For example, if their aromatic rings lie parallel to the silicate sheets, intercalated arylammonium ions are oxidized by atmospheric oxygen. The type of product formed depends on the charge density of the silicate anion. Thus, with a low charge (x = approx. 0.33), aniline is oxidized to a red ion, with a somewhat higher charge (x = approx. 0.55) to a bluish purple ion, and with a still higher charge, finally, to aniline black [64]. The oxidation products are displaced from the silicate lattice by alkaline solutions. They can be obtained in pure form by extraction with ether.

In all cases, the oxidizing agent is atmospheric oxygen, which diffuses through the hollows between the arylammonium ions. The high oxidation potential is probably related to a strong deformation of the electron shell by the silicate layers. As *Simon* has established, molecular oxygen loses its paramagnetic properties in the narrow passages within the zeolite mineral chabazite [65].

Oxidation of aromatic diamine derivatives yields semiquinones [66]. The deep color of these products attracted interest long ago, and it has since served as the basis of a rapid test for the presence of montmorillonite in mineral mixtures [67]. The formation of semiquinones, however, is not a specific reaction. Other silicates with large surfaces, such as kaolinite, also give a positive test [68].

Another reaction is the proteolytic action of highly charged mica-type layer-silicates with exchangeable hydronium ions. At low sheet charges, proteins are bound reversibly by cation exchange reactions; at higher charge densities on the silicate layers, the proteins are split into peptides and amino acids. The fragments from this cleavage are less strongly bound within the interior of the crystal than unaffected protein cations.

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[51] *O. Talibudeen*, Nature (London) *166*, 236 (1950).

[52] *A. D. McLaren* and *G. H. Peterson*, Nature (London) *192*, 960 (1961).

[53] *G. F. Walker* and *W. G. Garrett*, Nature (London) *191*, 1389 (1961).

[54] *O. Sieskind*, C. R. hebd. Séances Acad. Sci. *250*, 2392 (1960).

[55] *I. D. Sedletskii* and *S. M. Yusupova*, Dokl. Akad. Nauk SSSR *46*, 27 (1945).

[56] *W. Immel*, Ph.D. Thesis, Technische Hochschule Darmstadt, 1960.

[57] *C. E. Weaver*, Clays and Clay Minerals *8*, 214 (1960).

[58] *A. Weiss* and *G. Roloff*, unpublished results.

[59] *A. Weiss* and *H. Strunz*, in the press.

[60] *H. Deuel*, *G. Huber*, and *R. Iberg*, Helv. chim. Acta *33*, 1229 (1950); *H. Deuel*, Clay Min. Bull. *1*, 205 (1952); see also *E. A. Hauser* and *J. Alexander*, Colloid. Chem. *7*, 431 (1951).

[61] *G. Brown*, *R. Greene-Kelley*, and *K. Norrish*, Clay Min. Bull. *1*, 205 (1952).

[62] *R. Schwarz* and *H. W. Hennicke*, Z. anorg. allg. Chem. *283*, 346 (1956).

[63] In this connection, see *U. Hofmann*, Ber. dtsch. keram. Ges. *39*, 272 (1962).

[64] *A. Weiss*, *I. Kantner*, *M. Eckel*, *G. Hofmann*, and *E. Michel*, Beiträge Silikoseforsch. Sonderband *3*, 45 (1960).

[65] *I. Aharoni* and *F. Simon*, Z. physik. Chem. (B) *4*, 175 (1929).

[66] *Ch. G. Dodd* and *S. Ray*, Clays and Clay Minerals *8*, 237 (1960).

[67] *E. A. Hauser* and *M. B. Leggett*, J. Amer. chem. Soc. *62*, 1811 (1940); *S. B. Hendricks* and *L. I. Alexander*, Amer. Soc. Agron J. *32*, 455 (1940); *H. Weil-Malherbe* and *J. Weiss*, J. chem. Soc. (London) *1948*, 2164; *R. C. Mielenz* and *M. E. King*, Proc. Amer. Soc. Test. Mater *51*, 1213 (1951); *W. W. Hambleton* and *G. G. Dodd*, Econ. Geology *48*, 131 (1953); *Ch. G. Dodd*, Clays and Clay Technology, Calif. Div. of Mines Bull. *169*, 105 (155).

[68] *J. Endell*, *R. Zorn*, and *U. Hofmann*, Angew. Chem. *54*, 376 (1941).

The nonspecific acid hydrolysis of proteins in aqueous solution becomes a subtratespecific reaction within layer silicates that are capable of swelling. The specificity depends, on the one hand, on the number and distribution of the negative charges in the silicate sheet, and, on the other, on the number and distribution of the ε-amino- and guanido groups in the protein. Plausible model conceptions can be developed for this phenomenon as well [64]. Investigations with these enzyme models are, however, made difficult by the fact that they are only slightly stable in the hydronium form, and, on storage, partial decomposition into a form containing hydroxoaluminum and magnesium cations occurs [69, 70].

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[69] *A. Weiss*, Z. anorg. allg. Chem. *297*, 232 (1958).

[70] *U. Hofmann* and *K. Frühauf*, Z. anorg. allg. Chem. *307*, 187 (1960).

(Halogenomethyl)pyridines and (Halogenomethyl)quinolines

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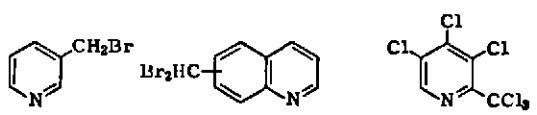
Hitherto, 2- and 4-trihalogenomethyl-pyridines and -quinolines were the only compounds of this type readily accessible by direct halogenation with free halogen. The particularly important and highly reactive monohalogenomethyl compounds had to be prepared by roundabout means, except in special cases. In the present article, a method is described for direct monochlorination of 2-methyl groups in heterocyclic bases on a technical scale. A review is also given of the preparation and properties of (halogenomethyl)pyridines and (halogenomethyl)quinolines.

I. Halogenation of Methylpyridines and Methylquinolines with Elemental Chlorine and Bromine

In the benzene series, chlorination and bromination of methyl groups takes a very clear course in most cases, and the mono-, di-, or trihalogenomethyl compound can each be prepared (*e.g.* from toluene), depending on the experimental conditions used. On the other hand, halogenation of methyl groups in the pyridine and quinoline series is beset with difficulties. The reactivity of any methyl group in these compounds is dependent upon its position relative to the nitrogen of the ring.

1. Known Methods

Dehnel [1] obtained the very unstable compound 3-bromomethylpyridine *(1)* by heating 3-methylpyridine in concentrated hydrochloric acid to 150 °C with bromine in a sealed tube; however he did not secure a pure specimen. *Drahowzal* [2] obtained 2-bromomethylpyridine from 2-methylpyridine using a modification of this method by heating the base in carbon tetrachloride and concentrated sulfuric acid at 160 °C in a sealed tube; again the pure compound was not isolated.



(1) *(2)* *(3)*

[1] *E. Dehnel*, Ber. dtsch. chem. Ges. *33*, 3498 (1900).

[2] *F. Drahowzal*, Mh. Chemie *82*, 794 (1951).

Mono- and dihalogenomethyl compounds can be prepared by rearrangement at high temperatures of the hydrobromide-perbromides of 5-, 6-, 7- or 8-methylquinolines, *i.e.* isomers with the methyl group in the carbocyclic ring [3–5].

Sell [6] obtained 2-trichloromethyl-3,4,5-trichloropyridine *(3)* together with 2-trichloromethyl-3,5-dichloropyridine from 2-methylpyridine hydrochloride at 105–110 °C. Similar results were obtained by *McBee*, *Hass* and *Hodnett* [7], who chlorinated 2-methylpyridine, 2,4-lutidine, 2,6-lutidine, and 2,4,6-collidine at increasing temperatures (50 to 180 °C) in the presence of a little water. All the methyl groups (in positions α and γ to the nitrogen of the pyridine ring) were chlorinated to trichloromethyl groups. Besides these trichloromethylpyridines, several trichloromethyl compounds of type *(3)*, which are chlorinated to a large extent in the ring, were also present in the reaction mixture. Formation of these by-products can be avoided by carrying out the halogenation in acetic acid in the presence of an alkali-metal acetate. This procedure was first used by *Königs* [8] for brominating 8-nitro-4-methylquinoline. *Hammick* et al. [9–12] developed the method further.

[3] *J. Howitz* and *W. Schwenk*, Ber. dtsch. chem. Ges. *38*, 1280 (1905).

[4] *J. Howitz* and *P. Nöther*, Ber. dtsch. chem. Ges. *39*, 2705 (1906).

[5] *J. Howitz* and *J. Philipp*, Liebigs Ann. Chem. *396*, 23 (1913).

[6] *W. J. Sell*, J. chem. Soc. (London) *87*, 799 (1905).

[7] *E. T. McBee, H. B. Hass*, and *E. M. Hodnett*, Ind. Engng. Chem. *39*, 389 (1947).

[8] *W. Koenigs*, Ber. dtsch. chem. Ges. *31*, 2364 (1898).

[9] *D. L. Hammick*, J. chem. Soc. (London) *1923*, 2882.

[10] *D. L. Hammick*, J. chem. Soc. (London) *1926*, 1302.

[11] *P. Dyson* and *D. L. Hammick*, J. chem. Soc. (London) *1939*, 781.

[12] *B. R. Brown, D. L. Hammick*, and *B. H. Thewlis*, J. chem. Soc. (London) *1951*, 1145.

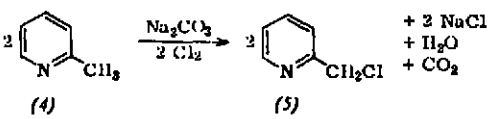
The alkali-metal acetate serves to neutralize the hydrogen halide formed [9], but it may also act catalytically [12]. 2-Tribromomethylquinoline is obtained in almost quantitative yield from 2-methylquinoline by this method [9]. The corresponding chloro compound can be also prepared, but in smaller yield [9]. This method can also be applied to substituted 2-methylquinolines, *e.g.* 5-, 6-, or 7-chloro-2-methylquinoline [13, 14]; however, it fails with 3- and 4-methylquinoline. Only the methyl group in the 2-position reacts with 2,3- and 2,4-dimethylquinoline, 2-tribromomethyl-3-methylquinoline [15] and 2-tribromomethyl-4-methyl-quinoline [12] being formed. If the nitrogen is quaternized, as in *N*-methyl-4-methylquinolinium iodide, then the methyl group in the 4-position is also attacked, and *N*-methyl-4-tribromomethylquinolinium bromide is formed [12]. 2-Methyl- and 4-methylpyridines are converted into the trichloromethyl compounds in 25 and 37% yields, respectively [11, 12].

Bromination fails in all cases with methylpyridines, and chlorination fails when the methyl group is in the 3-position. Mono- and dihalogenomethyl compounds cannot be prepared by this procedure [9–12]. The dibromomethyl compound too is secured only with some substituted 2-methylquinolines, *e.g.* 8-nitro-2-methylpyridine [10].

2. A New Method for Direct Chlorination of 2-Methyl Groups [*]

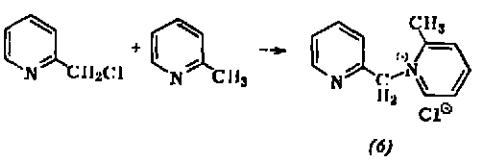
Up until now, 2-chloromethylpyridine and 2-chloromethylquinoline were not accessible by direct chlorination of the methyl compounds. A reaction does occur at first when attempts are made to chlorinate 2-methylpyridine in carbon tetrachloride at about 60 °C but comes to a halt after uptake of about one-third of the quantity of chlorine required for the formation of the monochloromethyl compound. On working up the product, only small quantities of 2-chloromethylpyridine are found, together with the hydrochloride of the starting material and tarry products. 2-Methylpyridine hydrochloride remains almost unattacked by chlorine either under these conditions or when irradiated with ultraviolet light. Probably salt formation with the hydrochloric acid produced in the reaction hinders the chlorination of the 2-methyl group. If the reaction is forced to take place by using higher temperatures, further chlorination of the monochloromethyl compound initially formed occurs, giving the trichloromethyl material. Moreover, the ring becomes partly chlorinated. Although the hydrochloric acid formed during the reaction is neutralized by the alkali-metal acetate when the chlorination is performed in acetic acid as described above, the weak acidity of the acetic acid is sufficient to cause exclusive formation of trichloromethyl compounds.

We therefore chlorinated 2-methylpyridine *(4)* in neutral solution at about 60 °C in the presence of acid-binding materials such as anhydrous sodium carbonate and obtained 2-chloromethylpyridine *(5)* in 65% yield, together with small quantities of di- and trichloromethylpyridine. During the reaction, about 2.5 moles of chlorine are taken up per mole of methylpyridine. The large excess of chlorine is used up partly by the sodium carbonate in conjunction with the water formed during the reaction and partly by over-chlorination and side-reactions. Over-chlorination has proved to be expedient:



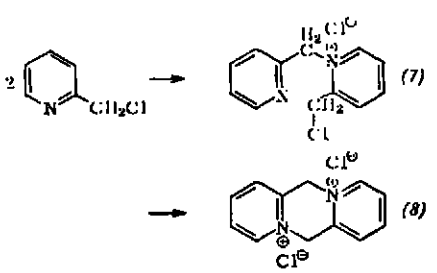
(4) *(5)*

unchanged starting material upsets the work-up, since, because of its instability, 2-chloromethylpyridine can be separated by fractional distillation from 2-methylpyridine only with difficulty or not at all. Moreover, the amount of tarry residues formed rises when the reaction is incomplete. It is probable that during the work-up 2-methylpyridine reacts with 2-chloromethylpyridine to form compounds of type *(6)*, which are transformed further on neutralization. 2-Halogenomethylpyridine and pyridine form corresponding



(6)

salts [16, 17]. The 2-chloromethylpyridine can also react with itself, but in this case salt formation is considerably more difficult, because the nitrogen of 2-chloromethylpyridine is significantly less basic than that of 2-methylpyridine. Polycyclic compounds *(8)* can



(7) *(8)*

even be obtained [18]. These undesirable side-reactions occur in neutral or weakly alkaline media and are strongly favored at high temperatures. It is therefore particularly important to maintain only a moderate temperature during the chlorination of 2-methylpyridine. The solvent also depresses salt formation by dilution. Moreover, it assists in dispersal of the heat of reaction and enables thorough mixing of the reacting substances

[13] *G. B. Bachman* and *D. Micucci*, J. Amer. chem. Soc. *70*, 2381 (1948).

[14] *A. M. Spivey* and *F. H. S. Curd*, J. chem. Soc. (London) *1949*, 2656.

[15] *B. R. Brown*, J. chem. Soc. (London) *1949*, 2577.

[*] Subject of German and foreign patent applications.

[16] *F. Kröhnke* and *K. F. Gross*, Chem. Ber. *92*, 22, 34 (1959).

[17] *B. R. Brown* and *J. Humphreys*, J. chem. Soc. (London) *1959*, 2040.

[18] *V. Boekelheide* and *W. Feely*, J. Amer. chem. Soc. *80*, 2220 (1958).

with the acid-binding material to be effected. Suitable solvents are neutral liquids, such as chloroform, carbon tetrachloride, and trichloroethylene, which react neither with chlorine nor with the chlorinated compounds. The monochloromethyl compound can be separated from the di- and trichloromethyl compounds formed as by-products by exploiting differences in basicity. Monochloromethylpyridine is extracted almost exclusively from the solution in carbon tetrachloride by 2 N hydrochloric acid. The dichloromethyl compound can be removed from the residue with concentrated hydrochloric acid. The trichloromethyl compound and other by-products remain in solution.

Preparation of 2-Chloromethylpyridine

Anhydrous sodium carbonate (600 g) is added to a solution of 2-methylpyridine (279 g = 3 moles) in CCl_4 (1500 ml), and the whole is heated at 60 °C with stirring. A steady stream of chlorine is then introduced at a rate of 88 g (= 1.24 moles) per hour. Crystals are often formed in the inlet tube and may block it. The temperature in the reaction vessel is maintained at 60 °C by cooling with a water-bath at approximately 45 °C. The chlorine is passed in for a total of 6 hours (528 g of Cl_2 = 7.5 moles). Towards the end of the reaction, the mixture becomes viscous and froths a little. After the mixture has cooled to room temperature, 3000 ml of water are added with vigorous stirring, causing the inorganic salts to dissolve. The pH of the aqueous phase lies between 6 and 8 and is brought to 8–9 by addition of 50–100 ml of 2 N NaOH. After repeated thorough mixing, the CCl_4 phase is separated off, and the aqueous phase extracted twice with 100 ml of CCl_4. The combined CCl_4 solutions are extracted once with 400 ml of 5 N HCl and then twice with 200 ml of 2 N HCl. The hydrochloric acid solutions (1040 ml.) are neutralized to pH 6–7 with a solution of 200 g of sodium carbonate in 500 ml of water. The yellowish-brown oil precipitated (about 240 ml) is separated off, and the aqueous phase is adjusted to pH 8 with further sodium carbonate solution and extracted three times with 100 ml of benzene. The precipitated oil and the benzene extracts are combined, dried with Na_2SO_4 and freed from benzene at room temperature under reduced pressure (water-pump). Distillation of the residue at 1.5 mm Hg affords (after a small fraction which is discarded) 249 g or 65 % of colorless 2-chloromethylpyridine, b.p. 45–47 °C, n_D^{20} = 1.5365; its picrate has m.p. 149–150 °C. The product quickly turns red and must be used immediately.

About 5 % 2-dichloromethylpyridine (b.p. 62–64 °C/1.2 mm; n_D^{20} = 1.5530; m.p. of picrate 117–118 °C) is obtained by extracting the CCl_4-solution with concentrated hydrochloric acid, neutralizing the hydrochloric acid solution, and extracting the oil precipitated with $CHCl_3$.

After extracting the dichloromethyl compound, small quantities of 2-trichloromethylpyridine (b.p. 76–80 °C/1.2 mm; n_D^{20} = 1.5620; no picrate) and of other compounds of unknown composition are still to be found in the CCl_4-residue. The trichloromethyl compound can be isolated from the neutralized CCl_4-solution by evaporation and fractional distillation of the residue.

Preparation of 2-Chloromethylquinoline

2-Methylquinoline (429.5 g = 3 moles) in CCl_4 (1000 ml) is treated with anhydrous sodium carbonate (300 g) and chlorinated in the same way as 2-methylpyridine, here 4 moles (= 284 g) of chlorine being sufficient to complete chlorination. When the reaction is over, 1250 ml of 2 N HCl are added with stirring to the cooled mixture, at first causing evolution of CO_2 from unused sodium carbonate. After thorough mixing, the aqueous phase is separated and the CCl_4-solution is extracted three times with 250 ml of 2 N HCl. The combined HCl-solutions are treated with a little activated charcoal, filtered, and neutralized to pH 7–8 with concentrated sodium carbonate solution. The 2-chloromethyl-

[19] *E. Maruszewska-Vieczorkovska* and *J. Michalski*, Roczniki Chem. *31*, 543 (1957); Chem. Zbl. *1959*, 9896.

[20] *W. Baker, K. M. Buggle, J. F. W. McOmie*, and *D. A. M. Watkins*, J. chem. Soc. (London) *1958*, 3594.

[21] *V. Carelli, M. Cardellini*, and *F. Liberatore*, Ann. Chimica *49*, 709 (1959); Chem. Zbl. *1961*, 12449.

Table 1. Compounds prepared by chlorination in carbon tetrachloride in the presence of sodium carbonate.

	B.p. [°C/mm Hg]	M.p. [°C]	n_D^{20}	Yield [%]	M.p. of picrate [°C]	M.p. of hydrochloride [°C]	Ref.
2-Chloromethylpyridine	45–47/1.5 73–76/10	—	1.5365	65	149–150 152–153 142–143	128 128–129 127	[27] [38] [20] [19]
2-Dichloromethylpyridine	62–64/1.2 90–92/15–16	—	1.5530	[a]	117–118	—	[11]
2-Trichloromethylpyridine	76–80/1.2 112–115/15 125–126/25	 –10	1.5620 1.5596 [b]	[a]	— —	— —	[11] [7]
2-Chloromethyl-3-methylpyridine	59–61/1.4	—	1.5407	64	146–146.5	157	—
2-Chloromethyl-4-methylpyridine	51–52/0.9	—	1.5326	44	159–160	—	—
2-Chloromethyl-6-methylpyridine	46/1.1 118–120/65 45–50/4	—	1.5315	57	160–161 162–164 161–162	155–156	[39] [20]
2-Chloromethyl-4,6-dimethylpyridine	68–70/1.4	—	1.5290	55	126–128	—	—
2-Chloromethylquinoline	—	56.5–57.5 54 54–55	—	86	171–172 172 168–169	190–192 (decomp.)	[12] [21]
2-Dichloromethylquinoline	—	82–83 82	—	[a]	118–119	—	[12]

[a] by-product [b] n_D^{35}

quinoline precipitated is filtered off, washed with water, and dried *in vacuo* at room temperature. An 86% yield (458 g) of a pale yellowish-brown product of m.p. 53–54 °C (picrate m.p. 165–169 °C) is obtained and can be used without further purification. Recrystallization from light petroleum gives a material of m.p. 56.5–57.5 °C (picrate m.p. 171–172 °C) which, like the crude product, discolors on storage.

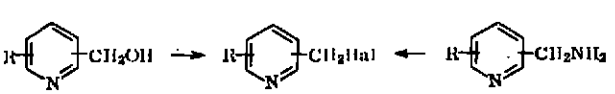
The CCl_4-solution is shaken with sodium carbonate solution to remove residual HCl, dried over Na_2SO_4, and evaporated at 30 mm. Hg. On cooling, the dark-brown residue obtained forms a cake of crystals which are recrystallized from isopropyl alcohol to give 24 g (4%) of 2-dichloromethylquinoline, m.p. 82–83 °C (picrate m.p. 118–119 °C).

The compounds listed in Table 1 were also prepared according to the method described for 2-chloromethylpyridine.

This method of chlorination can be applied to numerous pyridine and quinoline derivatives bearing a methyl group in position 2. Monochloromethyl compounds prepared in this way are listed in Table 1. The reaction proceeds particularly well with quinaldine, which can be converted into the monochloromethyl compound in 86% yield. Methyl groups in positions 3 or 4 are attacked only very slightly or not at all. Chlorination of both the methyl groups in the α-position to the ring nitrogen might by expected with 2,6-lutidine and 2,4,6-collidine, but this is not the case. As soon as one of these methyl groups has reacted to form a monochloromethyl group, the second methyl group can no longer be chlorinated under these conditions.

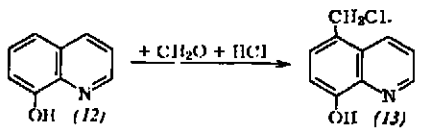
II. Indirect Methods of Synthesis

Since (halogenomethyl)pyridines and (halogenomethyl)-quinolines can be prepared conveniently in only a few cases by direct halogenation of the methyl groups, numerous attempts have been made to secure these interesting substances in other ways. The best-known method involves halogenation of hydroxymethyl compounds *(9)* with thionyl chloride [22, 23], phosphorus halides [12, 24, 25], or hydrohalic acids [17, 26]. This method leads to (monohalogenomethyl)pyridines and



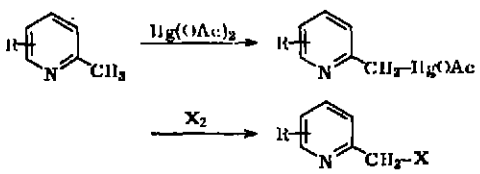
(9) *(10)* *(11)*

(monohalogenomethyl)quinolines *(10)*, is generally applicable, and almost always gives very high yields. The monohalogenomethyl derivatives *(10)* may also be prepared by treating aminomethylpyridines *(11)* with $NaNO_2$ in hydrochloric acid [27]. Chloromethylation has not yet been achieved with unsubstituted pyridines and quinolines, but it does take place when the benzene nucleus of quinoline bears certain substituents, *e.g.* with 8-hydroxyquinoline*(12)* [28, 29]. According to *Ukai*



(12) *(13)*

[30], monohalogenomethyl compounds are obtained by halogenation of the methylmercury derivatives which are formed from methylpyridines and mercuric acetate by spontaneous rearrangement of the initial adducts. The method appears to be limited to methyl groups



in position 2. *Walker* [31] obtained a good yield of α-(1-bromoethyl)pyridine by bromination of 2-ethylpyridine with *N*-bromosuccinimide. *Buu-Hoi* [32] reports the use of *N*-bromosuccinimide with methylpyridines and methylquinolines, albeit without giving experimental details. Interaction of 8-methylquinoline with this brominating agent [33] affords 8-bromomethylquinoline without difficulty, together with a small amount of 8-dibromomethylquinoline; from lepidine, the very unstable compound 4-bromomethylquinoline is formed [34]. On the other hand, only a 2% yield of 2,6-di(bromomethyl)pyridine [26] is obtained from 2,6-lutidine in this way.

Di- and monohalogenomethyl compounds can be prepared by reducing trihalogenomethyl compounds with tin in hydrochloric acid [10–12] or by boiling them with tetralin, xylene, mesitylene, or cyclohexene [35, 36].

Campbell and *Teague* [37] assume that 2-bromomethylpyridine is an intermediate in the formation of 1,2-di(pyrid-2-yl)ethane by the reaction of bromine on 2-picolyl-lithium. *Barnes* and *Fales* [26] obtained a very small yield (1%) of 2,6-di(bromomethyl)pyridine from 2,6-lutidine with phenyllithium and bromine.

Methylpyridine *N*-oxides are also suitable for preparing monochloromethyl compounds. According to *Matsu-*

[22] *H. S. Mosher* and *J. E. Tessieri*, J. Amer. chem. Soc. *73*, 4925 (1951).

[23] *K. Winterfeld* and *K. Flick*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *289/61*, 448 (1956).

[24] Swiss Patents 251023 and 251026 (both June 4th, 1946) Hoffmann La Roche; Chem. Zbl. *1950* I, 1883.

[25] *T. Kametani, K. Fukumoto*, and *Y. Nomura*, Chem. pharmac. Bull (Tokyo) *6*, 467 (1958); Chem. Zbl. *1962*, 2352.

[26] *R. A. Barnes* and *H. M. Fales*, J. Amer. chem. Soc. *75*, 3830 (1953).

[27] *J. Overhoff, J. Boeke*, and *A. Gorter*, Recueil Trav. chim. Pays-Bas *55*, 293 (1936).

[28] *Q. Fernando, W. L. W. Ludekens*, and *K. Gnanasoorian*, Analytica chim. Acta *14*, 297 (1956); Chem. Zbl. *1959*, 13794.

[29] *J. H. Burckhalter* and *R. J. Leib*, J. org. Chemistry *26*, 4078 (1961).

[30] *T. Ukai*, J. pharmac. Soc. Japan *51*, 73 (1931); Chem. Zbl. *1931* II, 2330.

[31] *B. H. Walker*, J. org. Chemistry *25*, 1047 (1960).

[32] *N. P. Buu-Hoi*, Liebigs Ann. Chem. *556*, 1 (1944).

[33] *B. Prijs, R. Gall, R. Hinderling*, and *H. Erlenmeyer*, Helv. chim. Acta *37*, 90 (1954).

[34] *K. N. Campbell, J. F. Ackerman*, and *B. K. Campbell*, J. Amer. chem. Soc. *71*, 2905 (1949).

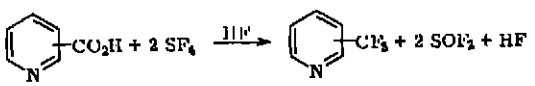
[35] *B. R. Brown* and *D. L. Hammick*, J. chem. Soc. (London) *1950*, 628.

[36] *B. R. Brown, J. O. Grice, D. L. Hammick*, and *B. H. Thewlis*, J. chem. Soc. (London) *1951*, 1149.

[37] *P. G. Campbell* and *P. C. Teague*, J. Amer. chem. Soc. *76*, 1371 (1954).

mura [38], good yields are obtained from 2-methylpyridine *N*-oxide and toluene *p*-sulfonyl chloride; according to *Kato* [39], only a small quantity is obtained as a by-product when phosphoryl chloride is used. *Kato* [39] obtained a small quantity of 2-chloromethyl-6-methylpyridine by treating 2,6-lutidine *N*-oxide with phosphoryl chloride. This reaction too is apparently limited to methyl groups in position 2.

2-Trifluoromethylpyridines can be prepared from trifluoroacetonitrile and 1,3-butadiene or 1,3-pentadiene, according to *Janz* and co-workers [40]. Compounds of the same type may be obtained by treating pyridinecarboxylic acids *(14)* with sulfur tetrafluoride in hydrogen fluoride, according to *Raasch* [41]. This reaction is successful with pyridine-2-, -3-, and -4-carboxylic



(14) *(15)*

acids and with quinoline-2-carboxylic acid. Interaction of trichloromethylpyridines with hydrofluoric acid in an autoclave is another route leading to trifluoromethylpyridines [7, 42].

Iodomethyl compounds could be isolated in only a few cases in the quinoline series; thus, *Howitz* [4, 43] obtained 8-iodomethylquinoline and 5-nitro-8-iodomethylquinoline by treating the corresponding bromine compounds with methyl iodide and with KI, respectively

III. Properties, Reactions, and Uses

The stability of the (halogenomethyl)pyridines and (halogenomethyl)quinolines known at present diminishes along the order of the halogen substituent F > Cl > Br > I. The number of halogen atoms in the halogenomethyl group also influences the stability, which falls from the tri- through the di- to the monohalogenomethyl compounds. Superimposed upon this picture is the influence of the position of the halogenomethyl group relative to the nitrogen of the ring, as well as the effect of further substituents.

The trihalogenomethyl compounds are usually very stable and may be stored without substantial decomposition. Their basicity is extremely weak; they give no picrates and no isolatable hydrochlorides. Carboxylic acids are readily obtained from them by hydrolysis.

[38] *E. Matsumura*, J. chem. Soc. Japan *74*, 363 (1953); Chem. Abstr. *48*, 6442 (1954).

[39] *T. Kato*, J. pharmac. Soc. Japan *75*, 1236, 1239 (1955); Chem. Abstr. *50*, 8665 (1956).

[40] *G. J. Janz* and *M. A. de Crecente*, J. org. Chemistry *23*, 765 (1958).

[41] *M. S. Raasch*, J. org. Chemistry *27*, 1406 (1962).

[42] U.S. Patent 2516402 (Sept. 4th, 1945) Purdue Research Foundation, Inventors: *E. T. McBee* and *E. M. Hodnett*; Chem. Zbl. *1951* I, 1527.

[43] *J. Howitz*, Ber. dtsch. chem. Ges. *35*, 1273 (1902).

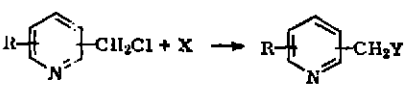
[44] U.S. Patent 2679453 (Oct. 10th, 1952), Inventors: *Ch. H. Brett* and *E. M. Hodnett*; Chem. Zbl. *1955*, 4680.

Trichloromethylpyridines have been proposed as weedkillers [44], and 2-chloro-6-(trichloromethyl)pyridine is recommended as an additive for fertilisers, because it inhibits waste of nitrogen by bacteria [45].

The dihalogenomethyl compounds are not very stable; they often become dark-brown on storage, and many resinify. They are weakly basic, form picrates and hydrochlorides, and can be extracted from organic solvents with concentrated hydrochloric acid. The dihalogenomethyl compounds are very resistant to hydrolysis by acids. Treatment with alkali gives only reddish-brown, resinous decomposition products. On the other hand, they can be converted very readily into aldehydes using silver nitrate.

The monohalogenomethyl compounds react with numerous substances (for examples see Table 2). The

Table 2. Reactions of monohalogenomethyl derivatives of pyridine and quinoline.



X	Y	X	Y
ROH	—OR	RCO_2Na	$—O_2CR$
RNH_2	—NHR	RSO_2Na	$—SO_2R$
R_2NH	$—NR_2$		
NaCN	—CN ($—CO_2H$, $—CO_2R$)	$NaCH(CO_2R)_2$	$—CH(CO_2R)_2$
NH_4SCN	—SCN		
RSH	—SR	$NaCH(CO—CH_3)(CO_2R)$	$—CH(CO—CH_3)(CO_2R)$
$S=C(NH_2)_2$	$—S—C(=NH)—NH_2$ → —SH	Na/xylene	$—CH_2—CO—CH_3$, $—CH_2—CO_2H$ → dimerization

products are of great interest, especially to the pharmaceutical industry. The monohalogenomethyl compounds are very resistant to hydrolysis by acids. Hydrolysis with alkali leads to intensely reddish-brown, resinous products of unknown composition. The monohalogenomethyl compounds react as bases, without of course attaining the basicity of the methylpyridines or methylquinolines. Their salts (*e.g.* hydrochlorides) are very stable and can be stored without decomposition. On the other hand, the free bases decompose readily, the bromomethyl compounds being considerably less stable than the chloromethyl derivatives. Generally they cannot be distilled and can only be used in solution. Only compounds with the chloromethyl group in position 2 are distillable, but only under mild conditions. However, even with these, thin-layer evaporators must be used for large quantities. The colorless distillate becomes intensely red after only a short time and in the course of a few days solidifies to a red crystalline mass. Alkyl groups in the pyridine ring raise the stability of these bases a little. The quinoline derivatives are also a little more stable. 2,6-Di(chloromethyl)pyridine also possesses

[45] Chem. Engng. News *40*, No. 12, 56 (1962).

considerable stability. Unlike the 2-chloromethylpyridines, the 3- and 4-chloromethylpyridines cannot be distilled. When attempts are made to evaporate solutions of these compounds, a crystalline mass is formed which probably consists of compounds of type *(7)* and their decomposition products. This salt-formation is exothermic and can take an extremely vigorous course. Thus, 3-chloromethylpyridine (prepared by neutralization of an aqueous solution of its hydrochloride with sodium carbonate and separation of the oil precipitated reacts with itself on standing at room temperature, developing heat until vigorous detonation occurs.

These halogenomethyl compounds cause intense inflammation of the skin, but this disappears after some time. Moreover, the free bases (especially in conjunction with solvents) cause strong irritation of the eyes and mucous membranes. When working with large quantities, it is therefore expedient to isolate not the halogenomethyl compounds, but rather their subsequent products.

Received, August 14th, 1962 [A 271/75 IE]

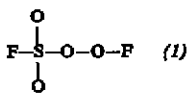
COMMUNICATIONS

Fluorosulfuryl Fluoroperoxide

By Dr. R. Gatti, Dr. E. H. Staricco, Dr. J. E. Sicre, and Prof. Dr. H. J. Schumacher

Instituto Superior de Investigaciones, Facultad de Quimica y Farmacia
Universidad Nacional de La Plata (Argentine)

On irradiating a mixture of fluorine monoxide and sulfur trioxide at room temperature with light of 365 mμ wavelength, fluorosulfuryl fluoroperoxide *(1)* is obtained in almost quantitative yield.



(1)

Compound *(1)* originates by stepwise reaction of a fluorine atom and an FO radical, formed primarily by photolysis of the fluorine monoxide, with a sulfur trioxide molecule. The $FSO_3\bullet$ radical is formed as an intermediate. The quantum yield of the reaction is 1.0 molecule/hν.

Compound *(1)* is a pale yellow-green liquid, b. p. 0 °C; its vapor pressure is given by $\log p_{(mm)} = 6.781 - 1063/T$. It is thermally stable at temperatures below 50 °C. Its infrared spectrum, its behaviour in neutral solution, and its oxidation value as measured against neutral aqueous KI solution all indicate the above structure.

Received, October 8th, 1962 [Z 399/223 IE]

Undecanolactam and Laurolactam from Cycloundecanoic Acid and Cyclododecanoic Acid

By Dr. W. Ziegenbein and Dr. W. Lang

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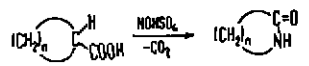
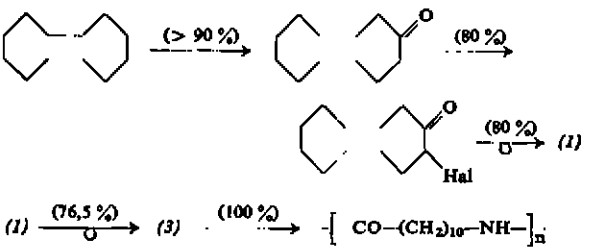
Chemische Werke Hüls AG., Marl (Germany)

Lactams with 11 or 12 carbons in their rings were formerly prepared from the cycloalkanones of corresponding ring size *via* the oxime [1]. The lactam with 11 carbon atoms in the ring is particularly difficult to obtain in this way. Starting from cycloundecanoic acid *(1)* [2] or cyclododecanoic acid *(2)* (prepared for example from 1,5,9-cyclodecatriene or cyclododecene *via* the formyl compound [3]), which were nitrosated with equimolecular quantities of nitrosylsulfuric acid in 15–30 % oleum at 65–70 °C in chloroform as solvent, we obtained undecanolactam (azacyclododecan-2-one) *(3)* or laurolactam (azacyclotridecan-2-one) *(4)* simply and in good yield.

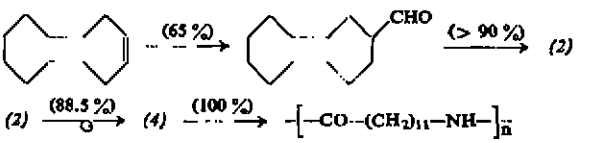


(1), n = 10 *(3)*, n = 10, m.p. 154,5 °C, Yield: 76,5 %
(2), n = 11 *(4)*, n = 11, m.p. = 150 °C, Yield: 88,5 %

This therefore suggests the following feasible new synthetic route to polyamide-11;



For polyamide-12:



Received, October 10th, 1962 [Z 368/251 IE]

[1] *L. Ruzicka, M. Kobelt, O. Häfliger,* and *V. Prelog,* Helv. chim. Acta *32,* 544 (1949); see also *G. Wilke* and *P. W. Borner,* German Pat. 1 075 601 (March 31st, 1959) Studiengesellschaft Kohle m.b.H.

[2] *W. Ziegenbein,* Chem. Ber. *94,* 2989 (1961); *R. Brockhaus,* unpublished results from Wissenschaftliches Laboratorium der Chem. Werke Hüls AG.; see also *P. Lafont* and *Y. Bonnet,* French Pat. 1 264 032 (May 6th, 1960), Soc. des Usines Chim. Rhône-Poulence.

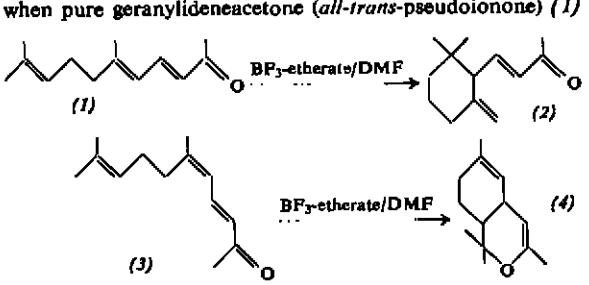
[3] *O. Glosauer, W. Schade,* and *W. Schneider,* unpublished results from Wissenschaftliches Laboratorium der Chem. Werke Hüls AG.; see also *G. Bo, P. Perras,* and *Y. Colleuille,* French Pat. 1 286 803 (Jan. 25th, 1961), Soc. des Usines Chim. Rhône-Poulence.

Preparation of γ-Ionone from all-trans-Pseudoionone

By Dr. G. Ohloff [*] and G. Schade

Max-Planck-Institut für Kohlenforschung
Abt. Strahlenchemie, Mülheim/Ruhr (Germany)

We have found [1], that γ-ionone *(2)* is formed in 33 % yield, alongside a lot of α-ionone and traces of β-ionone, when pure geranylideneacetone (*all-trans*-pseudoionone) *(1)*



is treated for 1 hour at room temperature with an equimolecular amount of BF_3-etherate. If 60 % diethyl ether or about 38 % dimethylformamide (DMF) is also added to the reaction mixture, then the γ-ionone fraction is increased to over 60 % of the cyclization product. Moreover, the composition of the product depends upon the reaction time and the temperature. Pure γ-ionone, which was obtained by fractional distillation of the reaction mixture through a highly efficient packed column equipped with a vapor-separating head and an automatically adjustable reflux-ratio device, isomerizes under the conditions of the cyclization to the same mixture of isomers as is obtained from *(1)*. Addition of more than 50 % of dimethylformamide to the BF_3-etherate inhibits the total cyclization reaction.

Nerylideneacetone *(3)* cyclizes almost exclusively to a mixture of the stereoisomeric bicyclic ethers *(4)* [2].

γ-Irone, γ-n-methylionone, γ-iso-methylionone and γ-allylionone were prepared from the corresponding open-chain *all-trans*-ketones in an analogous way by the use of the new cyclization procedure.

Received, October 24th, 1962 [Z 377/231 IE]

[*] Communication No. II on Cyclizations; Communication No. I: *G. Ohloff*, Liebigs Ann. Chem. *606*, 100 (1957).

[1] Application has been made for patents covering several variants of the process.

[2] This anomalous cyclization reaction was observed on pseudoirone by *Y. R. Naves* and *P. Ardizio*, C. R. hebd. Séances Acad. Sci. *235*, 579 (1952).

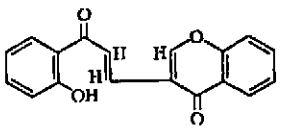
Dimerisation of Chromone

By Prof. Dr. A. Schönberg and Dr. E. Singer

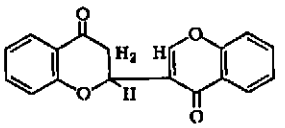
Fakultät für Allgemeine Ingenieurwissenschaften
der Technischen Universität Berlin (Germany)

Treatment of chromone in absolute ether at room temperature with sodium ethoxide and decomposition of the reaction product with dilute acetic acid yield yellow α-(chromon-3-yl)-β-salicoylethylene *(1)*, m.p. 173–174 °C. Compound *(1)* gives a positive ferric chloride reaction and yields salicylic acid with hydrogen peroxide in alkaline medium. Treatment of *(1)* in glacial acetic acid with concentrated sulfuric acid produces colorless 2-(chrom-on-3-yl)chromanone *(2)* of m.p. 154–155 °C. This conversion is reversible.

The infrared spectrum of *(2)* contains two carbonyl bands at 1685 cm^{-1} (compare flavanone: $\nu_{C=O}$ = 1680 cm^{-1}) and at 1638 cm^{-1} (compare 3-methylchromone: $\nu_{C=O}$ = 1640 cm^{-1}). The NMR spectra of *(1)* and *(2)* agree with the proposed structures. Dimeric chromones of type *(1)* were also obtained from 6-methylchromone and 7,8-benzochromone.



(1)



(2)

The data concerning infrared spectra refer to compounds in their crystalline state (pellets in KBr).

Received, December 10th, 1962 [Z 418/244 IE]

Tris-silylamines Containing Si-Functional Groups

By Dr. H. Niederprüm

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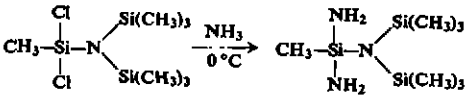
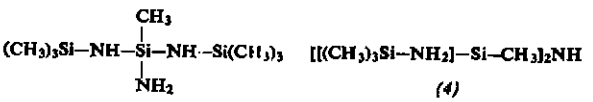
N,N-Bis-(trimethylsilyl)-methyldichlorosilylamine *(1)* can be prepared in 75 % yield from C_6H_5Li, $(CH_3)_3Si-NH-Si(CH_3)_3$, and CH_3SiCl_3 in a one-step reaction [1, 2]. It reacts with NH_3 at 0 °C to form the remarkably stable diamino compound *(2)*.



(1), B.p. 98 °C/13 mm Hg, m.p. 72–76 °C

(2), B.p. = 101 °C/17 mm, m.p. = 50–53 °C

Heating *(2)* to 200 °C results in isomerization to *(3)*, which partially condenses to *(4)*, b.p. 123 °C/0.3 mm, n_D^{20} = 1.4461,

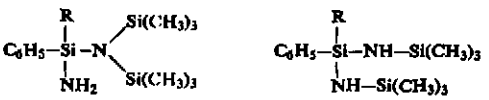


(3), B.p. 40 °C/0.4 mm, n_D^{20} = 1.4354

(4)

with elimination of ammonia. Careful hydrolysis of *(1)* or *(2)* gives the thermally unstable compound *N,N*-bis-(trimethylsilyl)-methyldihydroxysilylamine *(5)*, n_D^{20} = 1.4580.

N,N-Bis-(trimethylsilyl)-phenyldichlorosilylamine *(6)* (b.p. 115 °C/1 mm, m.p. 38–40 °C) is prepared similarly to *(1)* and reacts with NH_3 to give primarily the monoamino compound *(7)*, b.p. 118 °C/1 mm, n_D^{20} = 1.5112; complete ammonolysis to the diamino compound *(8)*, b.p. 105 °C/1 mm, n_D^{20} = 1.5084, takes place only on prolonged treatment with NH_3. On heating to 200 °C, both *(7)* and *(8)* rearrange by silyl migration; condensation and fission reactions are also observed.



(7), R = Cl
(8), R = NH_2

(9), R = Cl, b.p. 123 °C/0.5 mm, n_D^{20} = 1.4930
(10), R = NH_2, b.p. 101 °C/0.5 mm, n_D^{20} = 1.4889

With water and triethylamine in dioxan, *(6)* gives *N,N*-bis-(trimethylsilyl)-phenyldihydroxysilylamine *(11)*, m.p. = 100–105 °C, which decomposes at *ca.* 80 °C with evolution of NH_3.

Received, December 12th, 1962 [Z 422/247 IE]

[1] *U. Wannagat* and *H. Niederprüm*, Z. anorg. allg. Chem. *308*, 337 (1961).

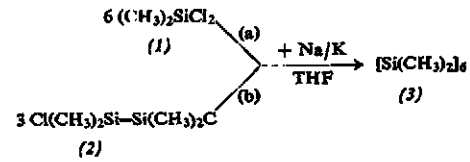
[2] Compounds *(1)*, *(2)*, *(6)*, and *(8)* were prepared simultaneously and independently by *U. Wannagat* and *H. Bürger* in Graz, Austria (personal communication).

Dodecamethylcyclohexasilane [1]

By Dr. U. Graf zu Stolberg [*]

Institut für Anorganische Chemie
der Universität München (Germany)

Sodium and dimethyldichlorosilane *(1)* in an autoclave are said to give some dodecamethylcyclohexasilane *(3)*, as well as polymeric $[Si(CH_3)]_x$ [2]. Under similar conditions, we found only polymeric products. However, treatment of *(1)* or tetramethyldichlorodisilane *(2)* [3] with a Na/K alloy in tetrahydrofuran produced *(3)* in high yield.



(1) *(2)* *(3)*

Reaction (a) takes place spontaneously when *(1)* is added dropwise into a suspension of Na/K alloy in very pure THF, applying the dilution principle; 138 g of *(1)* gave 50 g (81 %) of *(3)* and 8 g (13 %) of insoluble high molecular-weight substances. Reaction (b) does not go to completion even after

refluxing for three days; *(3)* was obtained in 31 % yield as the sole product. Compound *(3)* crystallizes in long colorless needles from methanol, m.p. 140 °C with a sharp transition-point at 74.5 °C, and sublimes from 120 °C. The formula of *(3)* was confirmed *inter alia* by its proton resonance spectrum. Apart from *(3)*, dodecaphenylcyclohexasilane is the only monomeric compound known with a six-membered silicon ring.

With iodine in equimolecular proportions, *(3)* gives 1,6-diiodododecamethylhexasilane (b.p. 185 °C/2 mm), as the main product. Compound *(3)* was split slowly by Na/K alloy in THF, soluble silanyl-alkali-metal compounds being formed; when the clear orange-brown solution obtained is added to trimethylchlorosilane in THF, straight-chain methyl-polysilanes $Si_n(CH_3)_{2n}{}^{+}{}_2$, where n = 2 to 5, and *(3)*, are produced and can be detected by gas chromatography. Similar results are obtained by treating the solution of silanyl-metal with methyl iodide or bromobenzene.

Received, December 13th, 1962 [Z 421/246 IE]

[*] Present address: Central Research Department, Experimental Station, E. I. Du Pont De Nemours & Co., Wilmington 98, Del., U.S.A.

[1] Communication No. 2 on methylpolysilanes. Communication No. 1, Angew. Chem. internat. Edit. *1*, 510 (1962).

[2] *C. A. Burkhard*, J. Amer. chem. Soc. *71*, 963 (1949).

[3] *M. Kumada* et al., J. org. Chemistry *21*, 1264 (1956).

Reaction between Pentafluorosulfur Chloride or Sulfur Tetrafluoride and Amines [1]

By B. Cohen and Prof. Dr. A. G. MacDiarmid [2]

John Harrison Laboratory of Chemistry,
University of Pennsylvania, Philadelphia, Penn. (U.S.A.)

Pentafluorosulfur chloride reacts with primary, secondary, and tertiary methylamines at low temperatures. With trimethylamine, a white solid adduct with the composition $SF_5Cl{\cdot}2(CH_3)_3N$ is formed at −78 °C. On warming to room temperature, one mole of SF_4 is liberated, and a solid residue is left. Analogous reactions apparently occur with dimethylamine and methylamine, but with these amines the adducts are much less stable and the SF_4 liberated at low temperatures combines readily with more amine. With CH_3NH_2, the new compound $CH_3N{=}SF_2$ is produced. Evidence for this reaction sequence is given by the fact that CH_3NH_2 combines directly with SF_4 at low temperatures to give good yields of $CH_3N{=}SF_2$:

$$3\,CH_3NH_2 + SF_4 \rightarrow CH_3N{=}SF_2 + 2\,CH_3NH_2{\cdot}HF$$

$CH_3N{=}SF_2$ is a colorless liquid, b.p. 16 °C, m.p. −123 °C; its infrared and mass spectra, molecular weight and analysis are consistent with the structure given above. The slightly impure material polymerizes rapidly at room temperature. $CH_3N{=}SF_2$ reacts further with CH_3NH_2 to give $CH_3N{=}S{=}NCH_3$:

$$CH_3N{=}SF_2 + 3\,CH_3NH_2 \rightarrow CH_3N{=}S{=}NCH_3 + 2\,CH_3NH_2{\cdot}HF$$

This substance also polymerizes slowly *in vacuo* at room temperature.

Received, December 14th, 1962 [Z 423/253 IE]

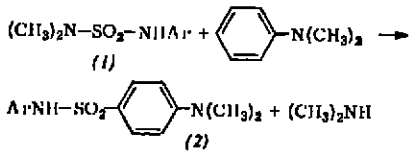
[1] Contribution from the Laboratory for Research on the Structure of Matter, University of Pennsylvania. The work was supported by the Advanced Research Projects Agency, Office of the Secretary of Defense. [2] Alfred P. Sloan Fellow.

The Synthesis of Sulfonamides from Trisubstituted Sulfamides

By Prof. Dr. F. L. Scott and Dr. W. A. Heaphy

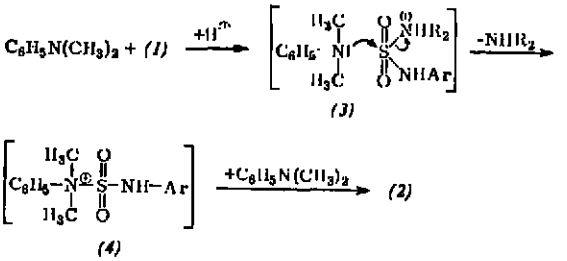
Department of Chemistry, University College, Cork (Ireland)

Trisubstituted sulfamides *(1)* react with excess *N,N*-dimethylaniline on refluxing for six hours to give 42, 59, 60, and 87 % yields of 4-dimethylaminobenzenesulfonanilides *(2)* where Ar = *p*-anisyl, phenyl, *m*-chlorophenyl, and 2-pyridyl, respectively. This reaction is not sensitive to *ortho*-substituents in the Ar moiety, for compounds with Ar = *o*-chlorophenyl and Ar = *o*-tolyl give yields of 61 and 44 %, respectively [1].



(1) *(2)*

The most probable mechanism for these and related [2] reactions involves a displacement process at the sulfonyl sulfur [3].



(3) *(4)*

The process displayed in *(3)* is akin to that encountered in the hydrolysis of related sulfur compounds [3], and the onium salt *(4)* is related to the amine/SO_3 complexes.

This reaction sequence explains why the rearrangements may be catalysed by acid – protonation facilitates bond-scission in *(3)* – and why the greatest yields of *(2)* are obtained when Ar contains an electron attracting group [this makes the sulfur atom more acidic and facilitates the formation of *(3)*].

The lack of reaction of tetrasubstituted sulfamides under our normal rearrangement conditions is also consistent with this mechanism; these sulfamides offer steric hindrance to the approach of base in process *(3)*.

Received, December 18th, 1962 [Z 430/248 IE]

[1] In the basic solvent, *(1)* undoubtedly forms the anion $(CH_3)_2NSO_2\overset{\ominus}{N}Ar$. This is very resistant to further attack by base. However, the sulfamide anion might undergo an elimination reaction to yield $(ArNSO_2)$, which would be solvated immediately to yield $Ar\overset{\ominus}{N}SO_2(CH_3)_2\overset{\oplus}{N}C_6H_5$, the conjugate base of *(4)*.

[2] *F. L. Scott, C. W. Schaumann*, and *J. P. King*, J. org. Chemistry *26*, 985 (1961).

[3] The lack of isotopic oxygen-exchange in the hydrolysis of ethylene sulfite (*C. A. Bunton* et al., J. chem. Soc. (London) *1958*, 4751), or between water and diphenyl sulfone, or between water and phenyl benzenesulfonate (*D. R. Christman* and *S. Oae*, Chem. and Ind. *1959*, 1251) suggest a displacement process at the sulfur atom rather than an addition-elimination sequence.

Synthesis of Polymethylenes from Carbon Monoxide and Hydrogen Using an Irradiated Ruthenium Catalyst

By Prof. Dr. H. Pichler and Dr. B. Firnhaber

Carl-Englet- und Hans-Bunte-Institut für Mineralöl- und Kohleforschung der Technischen Hochschule Karlsruhe (Germany)

Reaction between CO and H_2 at high pressure and as low a temperature as possible in presence of an alkali-treated ruthenium catalyst gives a product at 148 °C containing 19.5 % unbranched paraffins with a mean molecular weight of 43600 [1]. The catalyst was made from a solution of potassium ruthenate by reductive precipitation with methanol. It consists of RuO_2, which is reduced to the metal before or at the beginning of the synthesis with hydrogen or with the synthesis gas.

Irradiation of such a RuO_2 catalyst in air or in an evacuated glass tube with γ-radiation from a ^{60}Co source (4×10^5 r/hr.) for 65 hours renders it unusually active against hydrocarbons. It reacts at room temperature with nonane, which glows and ignites to give CO_2 and water. Unirradiated RuO_2 does not react with nonane. If the radiation-activated RuO_2 catalyst is introduced into nonane and filled with it into an autoclave, and the mixture compressed with the synthesis gas, then at 1000 atm and 132 °C much more hydrocarbons are is formed per unit of time from CO and H_2 than with a catalyst not subjected to previous irradiation.

The product of the synthesis was dark-colored. Infrared spectroscopy showed characteristic paraffin bands, plus further bands at 1730 cm^{-1} indicating groups containing oxygen, and at 2000–2100 cm^{-1} which are probably attributable to metal carbonyls. Pure white paraffins were obtained by treatment of the product with hydrogen at 150 °C and 200 atm and were fractionated by cooling their solution in toluene. At 85 °C, 27.4 % of the total paraffin was insoluble; this fraction had a mean molecular weight of 51900. At 88 °C, 9.4 % of the total was insoluble and had a mean molecular weight of 84700.

The dark compounds obtained before treatment with hydrogen seem to constitute the first instance of isolation of an organometallic intermediate in this hydrocarbon synthesis. Separation of this intermediate into metal and hydrocarbon cannot be effected by extraction but does take place by the action of hydrogen. This is important from the standpoint of the reaction mechanism.

Received, December 18th, 1962 [Z 416/249 IE]

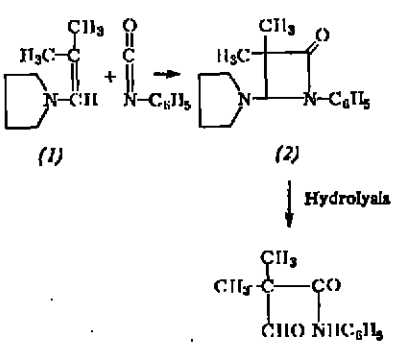
[1] First publication: *H. Pichler*, Brennstoff-Chem. *19*, 226 (1938): see *H. Pichler* and *H. Buffleb*, ibid. *21*, 257, 273, 285 (1940); *E. Hofmann*, diploma thesis, Technische Hochschule Karlsruhe, 1957; *A. Besold*, Ph.D. thesis, Technische Hochschule Karlsruhe, 1961.

β-Amino-β-lactams

By Doz. Dr. G. Opitz and cand. chem. J. Koch

Chemisches Institut der Universität Tübingen (Germany)

β-Amino-β-lactams are readily obtained by cyclo-addition of isocyanates onto β,β-disubstituted vinylamines.



(1) *(2)* *(3)*

1-Pyrrolidino-isobutene *(1)* and phenylisocyanate react exothermically to give an 84 % yield of 3,3-dimethyl-1-phenyl-4-pyrrolidino-azetidin-2-one *(2)*, m.p. 54 °C. Hydrolysis with 0.1 N HCl leads to 2-formyl-2-methyl-propioanilide *(3)*, m.p. 59–61 °C, m.p. of 2,4-dinitrophenylhydrazone 147–148 °C. The monoanilide [1] (m.p. and mixed m.p. 132 °C) of dimethylmalonic acid was obtained by oxidation of *(3)* with permanganate in pyridine, and isobutyranilide (m.p. and mixed m.p. 106–107 °C) by subsequent decarboxylation.

At 50–70 °C, phenylisocyanate reacts analogously with 1-morpholino-isobutene to give 3,3-dimethyl-4-morpholino-1-phenylazetidin-2-one, m.p. 98–99 °C, in 95 % yield, with 1-piperidinylisobutene to give 3,3-dimethyl-1-phenyl-4-(1'-piperidinyl)azetidin-2-one, m.p. 56 °C, in 92 % yield, and with 2-ethyl-1-morpholino-but-1-ene to give 3,3-diethyl-4-morpholino-1-phenylazetidin-2-one, m.p. 103–104 °C, in 94 % yield; with 1-morpholino-isobutene, α-naphthylisocyanate gives 3,3-dimethyl-4-morpholino-1-α-naphthyl-azetidin-2-one, m.p. 96 °C, in 85 % yield.

These cyclo-addition products decompose into their components when attempts are made to distil them. Their infrared spectra all show a lactam band at 1730–1750 cm^{-1}. Enhancement of the reactivity of the N–C–N grouping by ring-strain is manifested by their ease of hydrolysis to the corresponding amido-aldehydes, *e.g. (3)*, and by their spontaneous reaction with compounds containing acidic hydrogen such as nitromethane and α-naphthol.

Received, December 21st, 1962 [Z 426/259 IE]

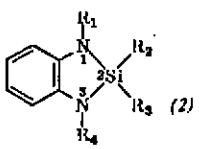
[1] *R. Scarpati, G. del Re*, and *T. Maone*, Rend. Accad. Sci. fisiche mat., Napoli *26*, 1 (1959). Chem. Abstr. *55*, 11423 (1961).

2-Silabenzimidazoline

By Dr. D. Kummer and Prof. Dr. E. G. Rochow

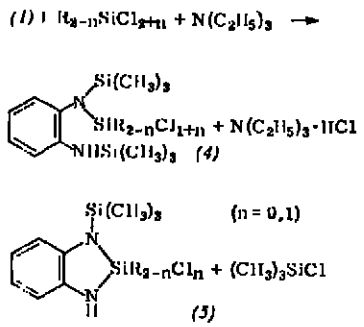
Harvard University, Cambridge, Mass. (U.S.A.)

On treatment with polyfunctional chlorosilanes in the presence of triethylamine and ether as solvent, *N,N'*-bis(trimethylsilyl)-*o*-phenylenediamine *(1)* yields compounds with a 2-silabenzimidazoline skeleton *(2)*.



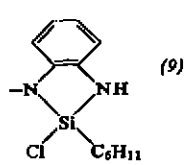
(2)

Thus, CH_3SiHCl_2 yields *(3)* where $R_1 = R_4 = Si(CH_3)_3$, $R_2 = CH_3$, and $R_3 = H$ in *(2)*, b.p. 85–86 °C/1 mm; $n_D^{20} = 1.5278$. With $(CH_3)_2SiCl_2$, CH_3SiCl_3, and $C_6H_{11}SiCl_3$, the reaction proceeds differently, even in the presence of excess triethylamine.



(4) *(5)*

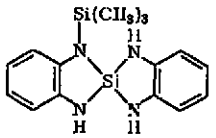
The following compounds were for instance obtained: *(5)*, where n = 0 and R = CH_3, m.p. 91–93 °C; *(6)*, where n = 1 and R = CH_3, decomposes with darkening above 99 °C; *(7)*, where n = 1 and R = cyclohexyl; *(8)*, where n = 0 and



(9)

R = cyclohexyl and *(9)* m.p. 187–189 °C (decomp.). All these compounds are very sensitive towards hydrolysis. The highly labile intermediates of type *(4)* have so far not been obtained pure.

With $SiCl_4$, the crystalline spiro-compound *(10)* (decomposes above 200 °C) is formed.



(10)

The compounds $C_6H_5SiCl_3$ and $(C_6H_5)_2SiCl_2$ fail to react under the conditions applied in the above synthesis.

Received, January 2nd, 1963 [Z 420/245 IE]

Base-Catalysed Fragmentations of Azo Compounds, a Route to the *o*-Bromophenyl Anion

By Dr. R. W. Hoffmann

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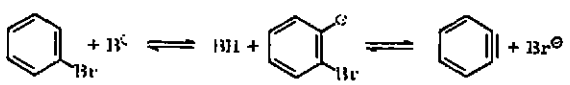
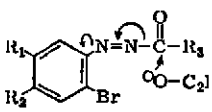
der Universität Heidelberg (Germany)

The *o*-bromophenyl anion *(1)* occurs as an intermediate stage in the equilibrium system [1]



(2) *(1)* *(3)*

In order to investigate the nature of *(1)* with regard to the formation of bromobenzene *(2)* and dehydrobenzene (benzyne) *(3)*, it is desirable to generate *(1)* independent of *(2)* and *(3)* and under conditions which do not permit reformation of *(1)* from *(2)* and *(3)*. This was achieved by an ethoxide catalysed fragmentation of compounds of type *(4)* in ethanol.



(4)

	R_1	R_2	R_3
a)	H	H	OC_2H_5
b)	H	H	C_6H_5
c)	CH_3	H	OC_2H_5
d)	H	CH_3	OC_2H_5

Treatment of *(4a)* at 40 °C and of *(4b)* at 20 °C each with half an equivalent of sodium ethoxide solution led to vigorous evolution of nitrogen and liberation of 7 % ionic bromine. Using gas chromatography, 75–85 % bromobenzene and 2–3 % phenetole were detected amongst the products, in addition to 58 % diethyl carbonate and 92 % ethyl benzoate, respectively. It is clear that the phenetole obtained can be formed only by addition of ethanol onto dehydrobenzene, because fragmentation of *(4c)* and *(4d)* yield 3- and 4-ethoxytoluene in the same ratio of 3:2 [2].

The ratio of the yield of bromobenzene to that of phenetole (≈ 30:1) and to that of bromide ion (≈ 10:1) gives an upper and lower limit, respectively, for the preponderance of protonisation of *(1)* over the loss of bromide ion from *(1)* [3]. Proton transfer to a phenyl anion is extremely rapid, hence the loss of bromide ion, although about 10–30 times slower, must also occur very rapidly. This is in accordance with other findings [3,4].

Received, January 2nd, 1963 [Z 425/256 IE]

[1] *G. Wittig* and *R. W. Hoffmann*, Chem. Ber. *95*, 2729 (1962).

[2] This isomer ratio is in agreement with that obtained by *G. Wittig* and *G. Vargas* for the addition of ethanol onto 3,4-dehydrotoluene (unpublished results).

[3] Cf. *J. D. Roberts* et al., J. Amer. chem. Soc. *78*, 601 (1956).

[4] *H. Gilman* and *R. D. Gorsich*, J. Amer. chem. Soc. *78*, 2217 (1956); *79*, 2625 (1957).

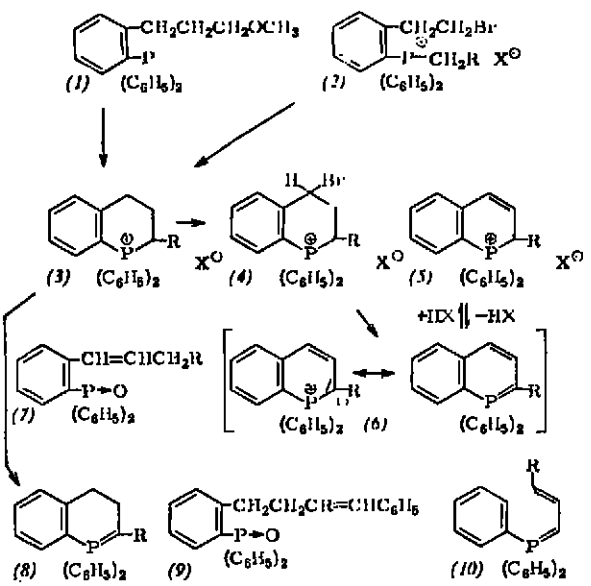
Cyclic Methylenephosphoranes [1]

By Dr. G. Märkl

Chemisches Institut der Universität Würzburg (Germany)

Cyclic phosphonium salts *(3)* required for the synthesis of six-membered rings containing an unsaturated methylenephosphorane group *(6)* were prepared a) by direct intramolecular quaternization [2] during cleavage of the ether *(1)* (m.p. 43–44 °C) with a mixture of hydrobromic and glacial acetic acids to give *(3)*, where R=H and X=$BF_4^\ominus$, m.p. 193–195 °C, in 74 % yield; or b) by intramolecular *C*-alkylation [1,3] of the intermediate methylenephosphorane *(3)* where R = C_6H_5 and X = $BF_4^\ominus$, m.p. 248–250 °C, obtained in 68 % yield from *(2)* where R = C_6H_5 and X = Br, m.p. 225–227 °C. The cyclic quaternary salts *(3)* can be smoothly converted into brominated phosphonium salts *(4)*, where R = H and X = $BF_4^\ominus$, m.p. 192 °C, 91 % yield or R = C_6H_5 and X = $BF_4^\ominus$, m.p. 195–197 °C, 86 % yield, using *N*-bromosuccinimide in boiling chloroform. Yellow (R = H) or orange-red (R = C_6H_5) solutions of the methylenephosphoranes *(6)* are obtained by treating *(4)* with sodamide in liquid ammonia and toluene or with potassium t-butoxide in dimethylformamide, which results in simultaneous dehydrobromination.

Salts *(5)*, where X = Cl, are formed by treatment of these solutions with gaseous hydrogen chloride; other salts *(5)* have R = H, X = $B(C_6H_5)_4^\ominus$ und m.p. 220–221 °C; or R = C_6H_5, X = $BF_4^\ominus$ and m.p. 178–180 °C.



A direct conversion of *(4)* into *(5)* does not occur, since *(4)* forms *(6)* even with 2 N NaOH in aqueous solution. The methylenephosphoranes *(6)* are precipitated from water as amorphous powders (R = H, yellow, λ_{max} = 362, 420 mμ (benzene); R = C_6H_5, orange-red, λ_{max} = 387, 426, 488 mμ). In contrast to its unusual stability towards hydrolysis – cleavage to give *(7)*, where R = H, m.p. 140–142 °C, occurs only in hot water – *(6)* is very sensitive to oxygen. In methanol (alkoxide method) in the presence of air, *(6)*, where R = H, forms several stable red- to violet-colored methylenephosphoranes within a short time; these can be separated by chromatography.

On consideration of other comparable methylenephosphoranes *(10)*, where R = H or C_6H_5, the ready formation of *(6)* and its stability can only be explained by a gain in resonance energy resulting from the attainment in the heterocyclic ring of cyclic conjugation involving the p_π–d_π double bond of the ylene. In accordance with the small participation of the ylide mesomeric form in *(6)*, formation of betaines with benzaldehyde or *p*-nitrobenzaldehyde and hence formation of olefins therefrom does not occur, even under drastic

conditions, although the dihydro compound *(8)* reacts smoothly with benzaldehyde to give *(9)*, where R = H, as an oil. The methylenephosphoranes *(6)* couple readily with diazonium salts [4] to give blue mono- and bisazo-compounds.

Received, January 2nd, 1963 [Z 427/260 IE]

[1] Second communication. – First communication: *G. Märkl*, Z. Naturforsch., in the press.

[2] Cf. *F. G. Mann*, J. chem. Soc. (London) *1951*, 411.

[3] *H. J. Bestmann*, Z. Naturforsch. *17b*, 78 (1962).

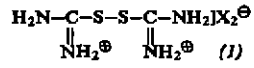
[4] *G. Märkl*, Tetrahedron Letters *1961*, No. 22, 807.

Di-(O,N-dialkylformimido) Disulfides

By Priv.-Doz. Dr. W. Walter and Dipl.-Chem. K.-D. Bode

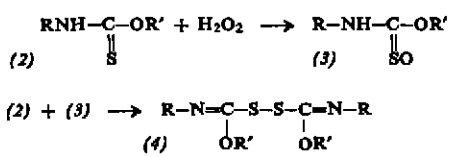
Chemisches Staatsinstitut. Institut für Organische Chemie der Universität Hamburg (Germany)

The salts of formamidine disulfides *(1)* prepared by oxidation of thiourea are known.



(1)

We have now found that *N*-monosubstituted thiourethans *(2)* may be oxidized to give di-(*O.N*-dialkylformimido) disulfides *(4)* with hydrogen peroxide. The thiourethan-*S*-oxide *(3)* occurring as an intermediate in the reaction may be identified by chromatography and spraying with ferric chloride.



(4a) R' = C_2H_5: m.p. = 98 °C

(4b) R' = C_3H_7: m.p. = 88–90 °C

R = C_6H_5

Besides *(4a)* and *(4b)*, the corresponding urethans are formed by oxidative desulfurization. It can be shown that an *S*-oxide also occurs as an intermediate step even with tertiary thiourethans by the appearance of a red-brown color with ferric chloride on oxidation of *N,N*-dimethyl-*O*-(*o*-nitrophenyl)thiourethan. This is due here to a 'labile peroxide' already postulated by *Billeter* [1].

It is remarkable that the disulfides *(4)* derived from *N*-substituted thiourethans are stable in the free state whereas only the salts can be prepared with analogous compounds of thiourethan *(1)*.

Received, January 14th, 1963 [Z 429/257 IE]

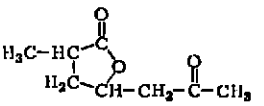
[1] *O. Billeter*, Ber. dtsch. chem. Ges. *43*, 1853 [1910].

The Action of Chloramine on *o*-Substituted Phenols

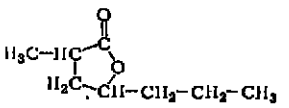
By Prof. Dr. W. Theilacker, Dr. K. Ebke, Dipl.-Chem. L. Seidl, and Dipl.-Chem. S. Schwerin

Institut für organische Chemie der Technischen Hochschule Hannover (Germany)

When phenoxides from 2,6-disubstituted phenols are treated in fused phenols with chloramine, colorless, stable, beautifully crystalline substances are obtained which are distillable *in vacuo* [1] and which we have considered as *O*-arylhydroxylamines, on account of their properties and rearrangement by mineral acids. The products resulting with mineral acid do not contain nitrogen but contain two additional oxygen atoms; on account of their properties and the products of their oxidative degradation, the constitution of 2-hydroxy-2,6-dialkyl-1,3-cyclohexanediones [2] was assigned to them. Detailed investigations have now established that the last-named compounds are in fact derivatives of γ-butyrolactone, *e.g. (1)*, chiefly since Clemmensen reduction yields an α,γ-dialkyl-γ-butyrolactone *(2)*.

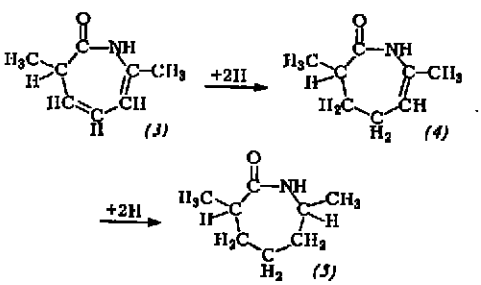


(1)



(2)

Further investigations then showed that the reaction products with chloramine are not *O*-arylhydroxylamines but doubly unsaturated ε-caprolactams of constitution *(3)*. The positions of the double bonds are confirmed by infrared and proton magnetic resonance spectra of the compounds *(3)–(5)* and by cleavage of *(3)* and *(4)* with mineral acids to yield nitrogen-free keto compounds.



(3) *(4)* *(5)*

Received, January 7th, 1963 [Z 431/258 IE]

[1] *K. Ebke*, Ph.D. thesis, Technische Hochschule Hannover 1959; see also *W. Theilacker* and *E. Wegner*, Angew. Chem. *72*, 131 (1960).

[2] *W. Theilacker*, Angew. Chem. *72*, 498 (1960).

The Action of Imidazole in Peptide Syntheses with Thiophenyl Compounds

Peptide Syntheses XXVII [1]

By Prof. Dr. Th. Wieland, Dr. H. Determann and cand. chem. W. Kahle

Institut für Organische Chemie der Universität Frankfurt/Main (Germany)

Thiophenyl compounds of acylated amino acids can serve as activated derivatives for peptide syntheses [2]. The possibility of using water as solvent seemed particularly advantageous, for it is then also possible to couple even free amino acids in the presence of weak bases such as pyridine [3]. Nevertheless, even after long heating, the yields only amounted to about 50%. We have now found that good yields of peptide can be achieved in the presence of imidazole under much milder conditions and without significant racemization.

Thus, 1.5 g (3.46×10^{-3} moles) of the thiophenyl ester of carbobenzoxyglycyl-L-phenylalanine (m.p. 104 °C) and 0.42 g (5.56×10^{-3} moles) of glycine in a solution of 10 g of imidazole in 3 ml of water were maintained at 40 °C for 1 hour. Work-up as described in the literature [4] afforded 1.2 g (88% of theory) of an oil of carbobenzoxyglycylphenylalanylglycine. On applying the *Anderson* test [5] to its ethyl ester, this was found to be the L-compound to over 95%.

Received, January 16th, 1963 [Z 432/261 IE]

[1] Communication No. 26: *Th. Wieland* and *K. Vogeler*, Angew. Chem. internat. Edit. *2*, 42 (1962).

[2] *Th. Wieland* and *W. Schäfer*, Angew. Chem. *63*, 146 (1951).

[3] *Th. Wieland* et al., Liebigs Ann. Chem. *573*, 99 (1951).

[4] *H. Determann*, *O. Zipp*, and *Th. Wieland*, Liebigs Ann. Chem. *651*, 172 (1962).

[5] *G. W. Anderson* and *F. M. Callahan*, J. Amer. chem. Soc. *80*, 2902 (1958).

A Nitrosyl Compound of Iridium

By Prof. Dr. L. Malatesta and Dr. Maria Angoletta

Terzo gruppo di ricerca del C. N. R.,
Istituto di Chimica Generale dell'Università di Milano (Italy)

Some halogenocarbonyl and metal halogenocarbonyl compounds of iridium have been reported recently [1,2], but no nitrosyl compounds were known hitherto. We have now found the first compound of this series, *viz.* potassium pentabromonitrosyliridiate-(III), $K[IrBr_5NO]$ *(1)*, small quantities of which are formed by the action of dilute nitric acid on $K_2[IrBr_6]$. Subsequently, we obtained *(1)* in almost quantitative yield by the reaction sequence

$$K_3[IrBr_6] + KNO_2 \rightarrow K_2[IrBr_4NO_2] + 2\,KBr$$
$$K_2[IrBr_4NO_2] + 2\,HBr \rightarrow K[IrBr_5NO] + KBr + H_2O.$$

Compound *(1)* is a stable, golden-brown, crystalline, diamagnetic compound which is soluble in water, alcohol, tetrahydrofuran, ethyl acetate, and acetonitrile. It behaves as a strong univalent electrolyte. Its infrared spectrum between 4000 and 700 cm^{-1} displays a single, intense absorption band at 1930 cm^{-1}, corresponding to the stretching vibration of the coordinated NO^+.

Compound *(1)* is the first of this type, in which the metal is in the oxidation state III, and the frequency of the NO stretching vibration fits in well with the following series of compounds in which the metal oxidation state increases from -I to III:

$K_3[V^{-I}(CN)_5NO]$: 1575 cm^{-1}; $K_3[Mn^{I}(CN)_5NO]$: 1730 cm^{-1};
$K_2[Ru^{II}Cl_5NO]$: 1905 cm^{-1}; $K[Ir^{III}Br_5NO]$: 1930 cm^{-1} [3].

Compound *(1)* is isosteric with and closely resembles $K_2[IrBr_5CO]$ (ν_{CO} = 2061 cm^{-1}) [2]. Both compounds exhibit remarkable stability toward heat and hydrolysis in spite of rather weak metal-nitrogen or metal-carbon linkages.

Received, January 17th, 1963 [Z 436/266 IE]

[1] *L. Malatesta* and *F. Canziani*, J. inorg. nucl. Chem. *19*, 81 (1961).

[2] *L. Malatesta* and *L. Naldini*, unpublished results.

[3] *C. G. Barraclough* and *J. Lewis*, J. chem. Soc. *1960*, 4842; *J. Lewis*, *R. J. Irving*, and *G. Wilkinson*, J. inorg. nucl. Chem. *7*, 32 (1958).

Surprisingly Stable Nitrogenous Free Radicals

By Prof. Dr. Richard Kuhn and H. Trischmann

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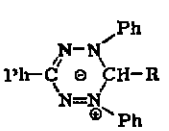
für Medizinische Forschung, Heidelberg (Germany)

By methylation and simultaneous or subsequent dehydrogenation (*e.g.* with atmospheric oxygen) of the red compound triphenylformazan, we have obtained a deep green paramagnetic radical $C_{20}H_{17}N_4$ *(1)* in 80% yield, which forms almost black prisms with a metallic lustre. Its electron spin resonance spectrum (*K. H. Hausser*) has nine lines, as is to be expected from the interaction of an unpaired electron with four almost equivalent nitrogen atoms. With benzyl bromide or *p*-bromobenzyl bromide compounds *(2)* and *(3)*, respectively, were obtained:



(1), R = H, m.p. 142—143 °C
(2), R = C_6H_5, m.p. 180—181 °C
(3), R = *p*-BrC_6H_4, m.p. 198—199 °C

Although comparable cyclic radicals are decomposed even by air or dilute acetic acid in the cold [1], compound *(1)* can be treated with mineral acid and boiled for a long time with acetic or conc. methoxide solution without decomposition. With $H^{\oplus}$, diamagnetic violet cations were obtained, *viz.* *(1)* without$^{\ominus}$:

$$2\,C_{20}H_{17}N_4 + HCl \rightarrow C_{20}H_{17}N_4^{\oplus}Cl^{\ominus} + C_{20}H_{18}N_4$$
green (paramagnetic) — violet (diamagnetic) — colorless (diamagnetic)

After acidification of a green solution of the radical, the absorption band of the violet solution rises to twice its original value on admission of air, because the leuco-compound $C_{20}H_{18}N_4$ is auto-oxidizable. The crystalline violet salts are formed immediately and quantitatively when, for example, a green solution of *(1)* in benzene is oxidized with bromine or iodine.

Although various mesomeric forms can be written using valence bonds and the octet rule, the high stability and ease of formation of the green radicals (verdazyls) is hard to explain, as the CH_2-group of *(1)* interrupts the conjugation in every case. Evidently energetic and geometric factors (symmetry) are much more important here.

Received, January 21st, 1963 [Z 434/262 IE]

[1] For example, pentaphenylpyrrolium perchlorate is very sensitive to O_2: *R. Kuhn* and *H. Kainer*, Chem. Ber. *85*, 498 (1952); and the 2,3-biphenylene-(2,2')-5-phenyltetrazolium radical is very sensitive towards $H^{\oplus}$ *inter alia*, *R. Kuhn* and *D. Jerchel*, Liebigs Ann. Chem. *578*, 1 (1952).

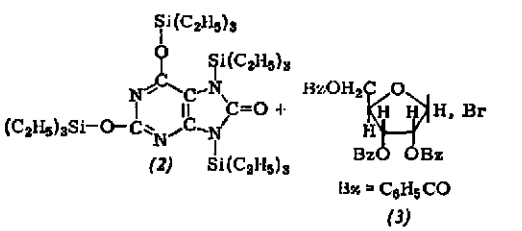
Syntheses of N-Glycosides Using Organosilicon Compounds

Uric Acid-3-ribofuranoside and Uric Acid-3-glucopyranoside [1]

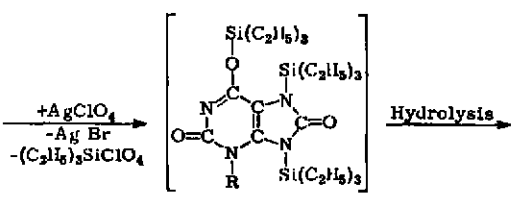
By Prof. Dr. L. Birkofer, Dr. A. Ritter
and Dipl.-Chem. H. P. Kühlthau

Institut für Organische Chemie
der Universität Köln (Germany)

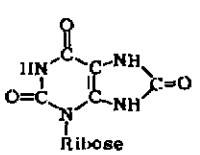
Davis, *Newton* and *Benedict* [2] isolated a riboside of uric acid from beef blood, which was identified as the 3-riboside *(1)* by *Forrest*, *Hatfield*, and *Lagowski* [3]. We synthetized *(1)* simply in 90% yield from tetrakis-triethylsilyluric acid *(2)* [4] and 2,3,5-tribenzoyl-1-bromoribose *(3)* [5] in the presence of silver perchlorate.



Bz = C_6H_5CO
(3)



R = 2,3,5-Tribenzoylribosyl



Ribose
(1)

By repeating the isolation of the natural 3-ribosyl uric acid from beef blood [3] we assured the identities of physical data

(infrared and ultraviolet spectra and optical rotation) of the natural and synthetic products.

Glycosidation of *(2)* was also effected when sodium iodide was used instead of silver perchlorate, or even without addition of either of these compounds, although then more vigorous reaction conditions were required. In this way we obtained a glucoside of uric acid from *(2)* and α-acetobromoglucose. This had the same ultraviolet spectrum (measured at pH 1, 7, and 14) as *(1)*. This product, so far unknown in nature, is therefore a 3-glucosyluric acid.

Received, January 23rd, 1963 [Z 435/263 IE]

[1] Communication No. 18 on organosilicon compounds; Communication No. 17: *L. Birkofer, A. Ritter,* and *W. Giessler,* Angew. Chem. internat. Edit. *2*, 96 (1963).

[2] *A. R. Davis, E. B. Newton,* and *S. R. Benedict,* J. biol. Chemistry *54*, 595 (1922).

[3] *H. S. Forrest, D. Hatfield,* and *J. M. Lagowski,* J. chem. Soc. (London) *1961*, 963.

[4] *L. Birkofer* and *A. Ritter,* Angew. Chem. *71*, 372 (1959); *L. Birkofer, H. P. Kühlthau,* and *A. Ritter,* Chem. Ber. *93*, 2810 (1960).

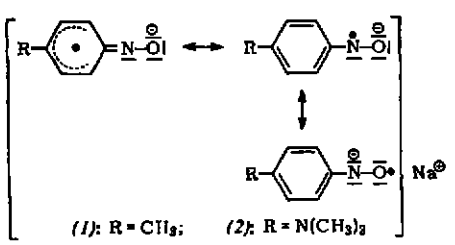
[5] *R. K. Ness, H. W. Diehl,* and *H. G. Fletcher Jr.,* J. Amer. chem. Soc. *76*, 763 (1954).

Stable Free Radicals Formed by Addition of Sodium onto Aromatic Nitroso Compounds

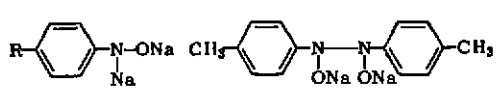
By Doz. Dr. T. Kauffmann and Dipl.-Ing. S. M. Hage

Institut für Organische Chemie
der Technischen Hochschule Darmstadt (Germany)

We have found that *p*-nitrosotoluene rapidly adds on one equivalent of sodium to form a deep green, apparently colloidal solution of the free radical *(1)* when shaken under nitrogen with powdered sodium in dry ether at 5–10 °C. The multilineal electron spin resonance spectrum [1] shows that the unpaired electron is located to a considerable extent in the benzene ring. The free radical *(1)* is converted by shaking for 1 hour with excess sodium into the reddish-brown substance *(3)*, which is insoluble in ether and which reforms the green radical when shaken with oxygen (0.5 mole).



(1): R = CH_3; *(2)*: R = $N(CH_3)_2$



(3): R = CH_3; *(4)*: R = $N(CH_3)_2$ *(5)*

The same reaction in tetrahydrofuran leads to a red solution of *(3)*, which is transformed to a clear deep-green solution of *(1)* by measured addition of oxygen. In this solution, about 25 % of the monosodium adduct exist in the free radical form (ESR measurement). Hence *(1)* is probably in equilibrium with a dimer *(5)*, which possesses no unpaired electrons. Hydrolysis of *(1)* gives a 48 % yield of 4,4'-azoxytoluene, very predominantly in the *cis*-form [2]; *N*-(*p*-tolyl)-hydroxylamine is formed by hydrolysis of *(3)*.

p-Nitrosodimethylaniline shows the same behaviour towards sodium as *p*-nitrosotoluene; the free radical *(2)* formed (ESR-spectrum) is bluish-green, and the compound *(4)* is red and has no free radical character. We have not yet succeeded in detecting a monosodium adduct of nitrosobenzene with an unpaired electron.

Received, January 29th, 1963 [Z 439/269 IE]

[1] See *T. Kauffmann* and *S. Hage,* Angew. Chem. *73*, 680 (1961).

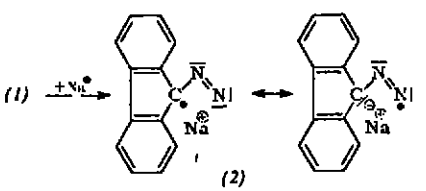
[2] *E. Müller,* Liebigs Ann. Chem. *495*, 132 (1932).

Stable Free Radicals Formed by the Action of Sodium onto Diazomethane Derivatives or Phenyl Azide

By Doz. Dr. Th. Kauffmann and Dipl.-Ing. S. M. Hage

Institut für Organische Chemie
der Technischen Hochschule Darmstadt (Germany)

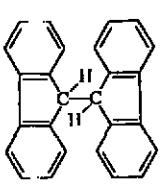
When its solution in ether is shaken under nitrogen at 20 °C with powdered sodium, diazofluorene *(1)* rapidly adds on a sodium atom to form a deep-blue free radical *(2)*, which is very sensitive to oxygen. According to electron spin resonance measurements, about 60 % of the sodium adduct exist in the free radical form. An equilibrium is therefore assumed between *(2)* and a dimer with no unpaired electron.



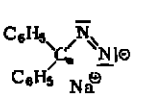
(2)

When *(2)* is hydrolysed under nitrogen, bifluorenyl *(3)* is formed in 32 % yield. Hydrolysis in the presence of oxygen gives 28 % bifluorenylidene and 34 % fluorenoneazine.

The deep-blue solution containing the free radical (ESR-spectrum) of the monosodium compound with the canonical form *(4)* obtained from diphenyldiazomethane [1] behaves similarly upon hydrolysis. Unlike other comparable free radicals [2, 3], the radicals *(2)* and *(4)* do not take up a second sodium atom under the reaction conditions stated.

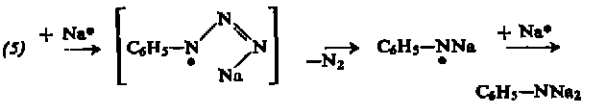


(3)



(4)

One mole of nitrogen is rapidly released from phenyl azide *(5)* by the action of powdered sodium in dry ether. The solution obtained contains free radicals (ESR spectrum) and forms hydrazobenzene upon hydrolysis. The further action of sodium leads to a red solution and an orange-red precipitate, from which aniline is formed by reaction with water, and a 51 % yield of diethylaniline by reaction with ethyl bromide. The probable reaction sequence is [4]:



Received, January 29th, 1963 [Z 440/270 IE]

[1] Phenyldiazomethane appears to form a monosodium compound which has an unpaired electron and which slowly loses nitrogen at room temperature.

[2] *W. Schlenk* et al., Ber. dtsch. chem. Ges. *47*, 474 (1914).

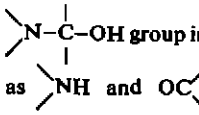
[3] *T. Kauffmann* and *S. Hage,* Angew. Chem. *73*, 680 (1961); Angew. Chem. internat. Edit. *2*, 156 (1963).

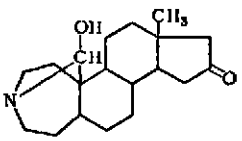
[4] *G. F. White* and *K. H. Knight,* J. Amer. chem. Soc. *45*, 1785 (1923), describe the color of the solution of disodium anilide (not conclusively established) in liquid ammonia as greenish-brown.

Constitution and Configuration of Cycloneosamandione [1]

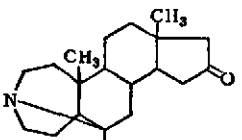
By Dr. G. Habermehl and Dr. S. Göttlicher

Institut für Organische Chemie and Eduard-Zintl-Institut der Technischen Hochschule Darmstadt (Germany)

Structures *(1)* and *(2)* have been considered for cycloneosamandione, an alkaloid isolated from the skin-gland venom of the fire salamander (*Salamandra maculosa* Laur.) [2]. The  group in these structures can react tautomerically as .

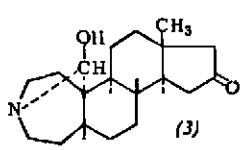


(1)

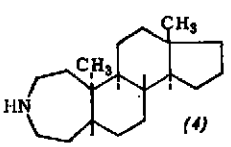


(2)

The infrared spectra of two derivatives of this "open" form, *viz.* *N*-acetylneosamandione and *N*-methylneosamandione iodomethylate, show that the carbonyl group which takes part in either an aldehyde ammonia or a ketone ammonia grouping in cycloneosamandione, is in fact an aldehyde group. Both compounds give a ν–CH + ω–CO combination band characteristic of an aldehyde group [3] at 2.30 μ (4350 cm^{-1}); the ν–CH-band of the aldehyde at 3.70 μ (2705 cm^{-1}), on the other hand, is well developed only in *N*-acetylneosamandione. We have investigated orthorhombic crystals of cycloneosamandione hydroiodide with X-rays (lattice constants: a = 10.87 Å, b = 9.59 Å, c = 19.51 Å; space group $P\,2_12_12_1$; four molecules per unit cell). A two-dimensional electron density projection along the b-axis indicated structure *(3)* for cycloneosamandione. The R_1-factor was 0.21. This indicates that cycloneosamandione has the same C,N skeleton as samandarine with the difference that the β-methyl group at C-10 in samandarine is replaced by an aldehyde group in the α-position in cycloneosamandione. The arrangement of the C and D rings as well as the absolute configuration were indicated moreover by the rotatory dispersion curve of cycloneosamandione (strong, negative Cotton effect at 325 mμ).



(3)



(4)

It is thus probable that a steroid with the anomalous configuration at C-10 has been found in nature for the first time. A three-dimensional structural determination is being performed.

It follows from structure *(3)* that the neosaman obtained by Wolff-Kishner reduction of cycloneosamandione by *Schöpf* and *Müller* has the structure *(4)*; its non-identity with the 3-aza-A-homo-5α- and -5β-androstanes prepared by *Shoppee* and *Krueger* [4] is therefore understandable.

Received, January 30th, 1963 [Z 438/267 IE]

[1] Communication No. 10 in the series "On samandarine and related alkaloids" begun by *C. Schöpf* and coworkers; Communication No. 9: *G. Habermehl*, Chem. Ber. *96*, (1963), in the press. This work will be published in full in Chem. Ber.

[2] *C. Schöpf* and *O. W. Müller*, Liebigs Ann. Chem. *633*, 127 (1960).

[3] *J. F. King* and *B. Vig*, Canad. J. Chem. *40*, 1023 (1962).

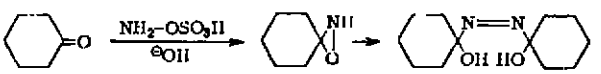
[4] *C. W. Shoppee* and *G. Krueger*, J. chem. Soc. (London) 3641 (1961).

A Semiaminal of Diimide

By Doz. Dr. Ernst Schmitz, Dr. R. Ohme and cand. chem. S. Schramm

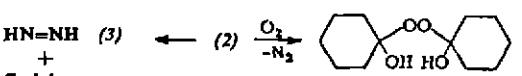
Institut für Organische Chemie der Deutschen Akademie der Wissenschaften, Berlin-Adlershof (Germany)

Formation of diimide on decomposition of hydroxylamine-*O*-sulfonic acid with alkali has been established [1]. Treatment of hydroxylamine-*O*-sulfonic acid with cyclohexanone in alkaline solution at 10 °C affords a 44 % yield of a crystalline compound which proves to be 1,1'-dihydroxyazocyclohexane *(2)*. An iso-oxime of cyclohexanone *(1)* occurs as an intermediate in the formation of *(2)*.



(1) *(2)*

Compound *(2)* can be regarded as a semiaminal of diimide. It decomposes rapidly even at room temperature into cyclohexanone, nitrogen, and hydrazine in the proportion 4:1:1. This decomposition proceeds by way of diimide *(3)*: decomposition in the presence of quinone gave hydroquinone in 49 % yield; analogously, azobenzene was reduced to hydrazobenzene in 55 % yield, the latter being identified as benzidine [2].



(4)

If *(2)* is stored with access to air at - 15 °C, the entire nitrogen content of the molecule disappears within several days. Di-1-hydroxycyclohexyl peroxide *(4)*, m.p. and mixed m.p. [3] 65–66 °C, is isolated in *ca.* 80 % yield.

Received, January 2nd, 1963 [Z 424/255 IE]

[1] *Ernst Schmitz* and *R. Ohme*, Angew. Chem. *73*, 807 (1961); *R. Appel* and *W. Büchner*, *ibid.* *73*, 807 (1961).

[2] Reductions with diimide: *S. Hünig*, *H. R. Müller*, and *W. Thier*, Tetrahedron Letters *1961*, 353; *E. J. Corey*, *W. L. Mock*, and *D. J. Pasto*, *ibid.* *1961*, 347; *E. E. van Tamelen* et al., J. Amer. chem. Soc. *83*, 3725, 3729 (1961).

[3] *N. A. Milas*, *S. A. Harris*, and *P. C. Panagiotakos*, J. Amer. chem. Soc. *61*, 2431 (1939).

Deutsche Gesellschaft für Mineralölwissenschaft und Kohlechemie (German Society for Petroleum Science and Coal Chemistry)

Karlsruhe (Germany), October 10th–13th, 1962

From the Proceedings:

Alkylation of Bituminous Coals

Carl Kröger (in collaboration with *H. G. Rabe*, and *Birgit Rabe*), Aachen (Germany)

Ethyl and propyl groups can be introduced into bituminous coals both by means of the Friedel-Crafts reaction and by heating the coal with ethylene and propylene under pressure at 300–360 °C. The quantities taken up depend on the experimental conditions and the nature of the coal. At the most, a threefold increase of the coal substance could be achieved. The properties of the coal (elemental analysis, thermal behavior, extraction and coking properties) are affected by the alkylation. An ether-soluble coal fraction is formed (up to 20%), and the pyridine solubility increases, albeit differently for the ethylated and propylated coals. This increase is due to splitting of the coal "molecule" caused by the alkylation. The molecular clusters present in the coal are also alkylated, and this process is followed by ring closure and dehydrogenation of both the newly synthetized aliphatic side chains and those already present in the coal to give aromatics. For this reason, the results for analysis of the ether extracts are found to be similar, even if different coal types are used as starting material for the alkylation.

Pyrolyses of Polynuclear Aromatic Hydrocarbons

K. F. Lang, *H. Buffleb*, and *M. Zander*, Castrop-Rauxel (Germany)

Pyrolysis of fused-ring aromatic hydrocarbons with two to four nuclei either in a tube filled with porcelain fragments heated at 750 °C or on electrically heated wire yields more highly condensed ring systems. With non-substituted hydrocarbons such as naphthalene, phenanthrene, and anthracene, direct nuclear condensation takes place under these conditions. On the other hand, with methyl-substituted aromatics such as α- and β-methylnaphthalene and acenaphthene, the molecules are joined preferentially through the methyl and methylene groups. One of the reactions in the pyrolysis of the fluorene is enlargement of the ring, so that 1,2,7,8-dibenzchrysene (tetrabenzonaphthalene) is obtained as the main product. It is very likely that the aromatics with four and more rings that occur in coal tar pitch are formed from lower aromatics by pyrolytic condensation during coking. In addition, polynuclear aromatics can also be formed from phenols, because pyrolysis of phenol or cyclohexanol leads to naphthalene, anthracene, phenanthrene, tetracene, and chrysene. Formation of these hydrocarbons must be preceded by splitting of the phenol molecule into C_2 and C_4 fragments, which combine together or with cyclohexene or benzene to give the above aromatics.

Preparation of Dimethyl Sulfoxide from Dimethyl Ether

H. Prückner, Wesseling (Germany)

Dimethyl ether, a by-product of the synthesis of methanol, is catalytically converted with hydrogen sulfide into dimethyl sulfide at 300–400 °C and atmospheric pressure. This is oxidized in the liquid phase with NO_2 (dissolved in dimethyl sulfoxide) to give nitrogen-free dimethyl sulfoxide. In this way, no dimethyl sulfide and very little NO_2 are lost. The yield is about 98%. Explosive mixtures of dimethyl sulfide or dimethyl sulfoxide with oxygen and explosive dimethyl sulfoxide/nitrogen dioxide or dimethyl sulfoxide/nitric acid adducts do not occur.

Dimethyl sulfoxide can dissolve many high polymers. A process for continuous polymerization of acrylonitrile in dimethyl sulfoxide has been developed, in which the poly(acrylonitrile) solution can be spun immediately afterwards. Dimethyl sulfoxide can also be used to separate phthalic acids from aromatic hydrocarbons, as solvent vehicle for color printing, and for applying antistatic finishes to synthetic fibers.

Purification of Olefins and Diolefins by Catalytic Hydrogenation in the Vapor Phase

M. Reich, Marl (Germany)

Olefins and diolefins are being produced in increasingly larger amounts by thermal cracking processes (pyrolyses). In order to prepare the complex mixture of hydrocarbons thus obtained for further treatment, it is necessary to separate it into fractions. This is generally achieved by distillation, extraction, or a combination of both methods. In this way, fractions are recovered with a degree of purity which is inadequate for many chemical processes. Compounds with acetylenic or cumulative or occasionally conjugated double bonds are particularly harmful. Selective catalytic hydrogenation has long proved efficacious for their removal. This can be carried out in the gas phase and, since recently, also in the liquid phase. If the fractions are separated by distillation, as is usually the case, it is possible to hydrogenate the still-head take-off in the gas phase (vapor-phase hydrogenation). Many selective catalysts are available for this. With these, almost complete conversion of even larger quantities of methylacetylene and propadiene into propylene is achieved with propylene fractions. Hydrocarbon streams containing butadiene are selectively freed of ethyl-, vinyl-, and methyl-acetylene. The life of the catalyst can extend from a few months to 1.5 years.

Recovery of Pure Benzene by Sulfuric Acid Refining

H. Ritter, Gelsenkirchen (Germany)

The selective sulfonation of thiophene as shown by the equation, is reversible at low thiophene concentrations (<100 mg/kg) and high water content of the sulfuric acid.

$$C_4SH_4 + H_2SO_4 \rightarrow C_4SH_3{-}SO_3H + H_2O$$

The equilibrium is approached from both sides much more rapidly than is to be expected from the old specifications. A continuous process has been developed, with which the thiophene content of benzene can be reduced to 2–20 mg/kg. The extracted thiophene is recovered with a loss of less than 1%.

The Average Size of the Condensed Aromatic Systems in Coal and Coal Extracts

E. de Ruiter and *H. Tschamler*, Brussels (Belgium)

Five independent physical methods can be used for determining the number of rings in fused-ring aromatic compounds: X-ray structural analysis, electrical conductivity,

light absorption in the ultraviolet and visible range, light absorption of a solution in concentrated H_2SO_4, and determination of the ratio of aromatic hydrogen to aromatic carbon in the unsubstituted aromatic system. The last two methods are new.

A coal sample and its pyridine, benzene, and petroleum ether extracts were examined. All samples show polymeric character but with different degrees of polymerization, and certainly do not consist of only one aromatic system of definite size (R_{ar}), hence only a mean value $\overline{R}_{ar}$ can be deduced. Comparison of the results from all five methods leads to the very satisfying conclusion that, for the coal and its extracts under investigation $\overline{R}_{ar} = 4 \pm 1$. The size of the individual aromatics probably lies between $R_{ar} = 1$ and $R_{ar} = 7$.

Relations between the Chemical Structure and the Sliding Properties of Selected Organic Compounds and Mineral Oils with Additives

G. Spengler and *F. Wunsch*, Munich (Germany)

In the region of low sliding velocities, slipping may proceed jerkily (relaxation oscillations or stick-slip motion). This can be prevented with lubricants. In order to determine the dependence of the behaviour under shear of a lubricant on its chemical constitution, a number of organic compounds and mineral oils with additives were investigated on the Tannert-Wieland friction meter. The coefficients of friction were determined at the start, during sliding (v_{max} = 0.025, 0.05, and 0.1 mm/sec.), and with decreasing velocity ($v \rightarrow 0$), and the amplitude of the stick-slip oscillations was measured.

With all the types of compound examined (n-paraffins, alcohols, n-carboxylic acids, monocarboxylic esters, dicarboxylic di-esters, adamantane-1-carboxylic esters, polyglycols, and tetra-alkyltin compounds) the anti-frictional behaviour improves with increase in the length of the hydrocarbon chain. The coefficients of kinetic friction decrease more slowly with liquid n-paraffins and the tetra-alkyltin compounds than with liquid monocarboxylic acids. Primary alcohols and technical polyglycols have high coefficients of kinetic friction and thus oppose the stick-slip motion only moderately. The magnitude of the coefficient of kinetic friction of the unbranched aliphatic mono- and di-carboxylic esters is influenced more by the chain length of the acid component than by that of the alcohol. The adamantane-1-carboxylic esters are poor lubricants.

Experiments on the possibility of influencing the lubricating properties of mineral oils with additives (benzyl chloride, carbon tetrachloride, benzoyl chloride, *p*-toluenesulfonyl chloride, dibenzyl disulfide, diphenyl sulfide, tricresyl phosphate, nitrobenzene, oleic acid) showed that only materials which react with the metal surface effected an improvement. No electrostatic charge and discharge of the sliding surfaces could be observed during stick-slip motion.

Removal of Carbon Dioxide from Cracking Gases Using Taurinate Solutions

R. Wirtz, Frankfurt/Main-Hoechst (Germany)

Depending on the conditions used in high temperature cracking processes for producing acetylene and ethylene from saturated hydrocarbons, carbon dioxide is formed in different quantities. The carbon dioxide can be scrubbed out with taurinate solutions before separating off the acetylene. Such taurinate solutions, *e.g.* potassium-n-methyltaurinate, bind the carbon dioxide chemically by forming carbamic acids. Since the reaction proceeds very rapidly and the absorption equilibrium is favorable, it is possible to scrub out the carbon dioxide down to a content of a few ppm. in only a single stage. In the technical process, carbon dioxide is absorbed from the raw gas at about 15 atm gauge pressure and 30 to 50 °C and stripped from the charged solution at normal pressure by low pressure steam. This requires 3–6 kg of steam per cubic meter of carbon dioxide (19–38 lbs. of steam/100 cft. of CO_2), depending on running conditions.

If saturated hot air is used for the regeneration instead of steam, a small amount of oxidation of the taurinate occurs. This oxidation can however be reduced considerably by inhibitors.

Potassium methyltaurinate solution displays high selectivity towards carbon dioxide and only very low solubility for acetylene and ethylene. The solution is not corrosive, and the plant equipment can be made of normal steel.

[VB 658/68 IE]

Symposium on Radioactive Dating

November 19th to 23rd, 1962, Athens (Greece)

From the Proceedings:

Dating of Meteorites

Meteorites are so far the only fragments of extra-terrestrial matter available on earth. Two questions are at present in the foreground of their investigation: how long was the meteorite exposed to cosmic radiation (cosmic ray exposure), and how long has the meteorite already been on earth (terrestrial age)?

E. Vilcsek and *H. Wänke* (Mainz, Germany) examined about 50 meteorite samples for their chlorine-36 and argon-39 contents in order to clarify this. Comparison of the data obtained with one another, and with determinations of other radioactive isotopes produced by cosmic radiation, permitted the estimation of the terrestrial age of meteorites. Values lying between a few hundred years and more than 1.5 million years were found. The cosmic ray exposure was found by comparison of the chlorine-36 and argon-39 measurements with rare gas determinations. This showed that the cosmic ray exposure of iron meteorites was usually much greater than that of stone meteorites. Examination of different samples from very large meteorites frequently gave different radiation exposures. This can be explained by the collision and fragmentation of the meteorites in space.

P. S. Goel and *T. P. Kohman* (Pittsburgh, Pennsylvania, USA) also investigated cosmic ray exposure using chlorine-36 measurements on 27 samples from 10 iron meteorites, also directing their attention to the distribution of the ^{36}Cl in the meteorite. The activities found were between 23 disintegrations/min·kg (Aroos) and 2.3 disintegrations/min·kg (Canyon Diablo). Only one value of a sample of the Ider meteorite was considerably lower *viz.* $\leqq 0.4$ disintegrations/min·kg. The ^{36}Cl values were compared with the content of rare gases. This showed that the calculated $^{36}Ar/^{36}Cl$ and $^{3}He/^{36}Cl$ exposure ages tended to vary considerably within a meteorite. This is because the concentration gradient for ^{36}Cl is appreciably greater than that for rare gases and that erosion in space also plays a part. The bulk of the stable products in a sample arose at a time when they were still relatively far in the interior, where the gradients are small, while the radioactive products were formed comparatively recently near the surface, where the gradients are large. From these considerations, the rate of erosion in space was estimated to be 0.02–0.10 cm per 10^6 years. If this is correct, the cosmic ray intensity must

formerly have been greater than it is now to give the present rare gas concentrations. If an exponential decrease in cosmic ray intensity such as $F(t) = F_0 e^{-t/\tau}$, is assumed, then τ must be or the order of 100×10^6–300×10^6 years.

According to investigations by *T. P. Kohman* and *P. S. Goel* (Pittsburg, Pennsylvania, U.S.A.), the terrestrial age of meteorites can also be determined by measurement of the cosmogenic carbon-14. In the case of stone meteorites, 10–40 g samples are subjected to oxidative fusion in a closed system. With iron meteorites, 150–400 g samples are dissolved in nitric acid and the bound carbon as well as any cosmogenic carbon are expelled by a stream of oxygen as CO_2; graphitic carbon remains behind. The ^{14}C activity for nine recently fallen stone meteorites was between 49 and 78 disintegrations/min·kg, the mean value being 62.5 disintegrations/min·kg. The differences are due chiefly to the oxygen content of the samples. Of eight meteorite finds examined, two have a terrestrial age of 3000–5000 years, the others contained less ^{14}C and have therefore been on earth a few thousand years longer. The Potter-Chondrite no longer contains any ^{14}C and must therefore have a terrestrial age of >21000 years, while the stony-iron meteorite Admire is 11000 ± 1500 years old. The ^{14}C content of recently fallen iron meteorites was 1.80 ± 0.25 disintegrations/min·kg (Aroos) and 1.66 ± 0.37 disintegrations/min·kg (Sikhote-Alin). The ratio ^{14}C to ^{10}Be is on the average 0.5 ± 0.1 and appears to be largely independent of the size of the meteorite and the depth of the sample.

The $^{14}C/^{10}Be$ ratio was used for dating iron meteorite finds and the ^{10}Be content was estimated from the ^{36}Cl content, where ^{10}Be was not measured directly. The terrestrial age of six meteorites varied between $\leq$4700 years (Henbury) and $\geq10^4$ years (Sardis). Because of its very low ^{36}Cl content, the age of Sardis is estimated at almost 10^6 years, while Ider is probably even longer than 1.6×10^6 years on earth.

It is possible to make a comparison between the cosmic ray intensity near the earth's orbit and the mean cosmic ray intensity over the whole meteorite path (which has a mean distance from the sun of about the order of three astronomical units), from the ratio of the cosmogenic argon isotopes ^{37}Ar (half-life 35 days) and ^{39}Ar (half-life 325 years) in freshly fallen meteorites. *R. Davis, Jr., R. W. Stoenner*, and *O. A. Schaeffer* (Brookhaven National Laboratory, U.S.A.) compared the $^{37}Ar/^{39}Ar$ ratio in four recently fallen meteorites with the production probability of those isotopes when bombarding meteorite samples with 3 GeV (3000 MeV) protons (generated in the cosmotron). The $^{37}Ar/^{39}Ar$ ratio is considerably influenced by solar flares occuring a few months before the meteorites fall. This effect was investigated by comparison of the ^{37}Ar determined in the steel of the satellite Discoverer 17 (started during the flare on November 12th, 1960) with ^{37}Ar generated by normal cosmic irradiation in the satellites Discoverer 18 and 26.

The long-lived isotopes aluminum-26 and beryllium-10 are suitable for the determination of very great meteorite ages. *E. H. Crevecoeur* (Louvain, Belgium) and *O. A. Schaeffer* (Brookhaven National Laboratory, U.S.A.) separated these isotopes from iron meteorites by removing iron, cobalt, vanadium, titanium, etc., by extraction, chromatography, or precipitation using classical methods. Al, Be, and rare earths were precipitated quantitatively by Cupferron reagent at pH 4.7. The aluminum was separated from the beryllium by precipitation with 8-hydroxyquinoline, and the beryllium purified by extraction and precipitation in the presence of ethylenediamine tetra-acetic acid. The yield was determined gravimetrically, and the activities of the solid samples measured with an end-window proportional counter. The results indicate that cosmic irradiation has been constant over the last 10 million years.

J. Zähringer (Heidelberg, Germany), determined the age of tektites by the potassium:argon ratio method. North American finds from Georgia, Texas and Massachusetts (Martha's Vineyard) all had an age of 34×10^6 years. Six Czechoslovakian tektites were aged 15×10^6 years, and 20 Indochinese-Australian tektite samples were all 0.6–0.7×10^6 years old. These age determinations must be considered particularly reliable, since tektites have been subjected to high temperatures at which all rare gases would have been able to escape, so that the entire argon-40 found must be considered to be the daughter element of potassium-40. However, tektites were also found which contained atmospheric, besides radiogenic argon. Two tektites from the Ivory Coast which have ages of about 10^6 years belong, among others, to this group. It is assumed on the basis of this correspondence in age that the North American tektites arose from one and the same incident. The Czechoslovakian tektites (moldavites) probably also owe their origin to a single occurrence. It is interesting to note that a K:Ar determination on glass from Suevite, from the Nördlinger Rieskessel (Germany) has shown that this material is the same age as moldavite (*W. Gentner* et al.). It thus appears possible that the moldavites and Rieskessel glass arose from the same incident. The radioactive datings were generally in good agreement with geological datings, whenever these were available.

Water Dating

G. S. Bien, N. W. Rakenstraw, and *H. E. Suess* (University of California, U.S.A.) dated deep sea water from the Pacific and Indian Oceans by means of the carbon-14 method. The ^{14}C concentration of water in the Pacific is practically constant below 1000 m and only rises a little in the neighborhood of the sea bed. In one case, a definite minimum was obtained for the ^{14}C content at a depth of 2000 m. There is a difference in age of about 400 years between water from about 40 degrees southern latitude and that from about 40 degrees northern latitude. This corresponds to a velocity component of the water in a northerly direction of about 0.05 cm/sec. The true value is possibly somewhat reduced by the fact that ^{14}C is added to the water by oxidation of organic substances at the sea bottom. Under these circumstances, a northerly velocity of about 0.03 cm/sec is more probable. Deep sea water from the Indian Ocean showed somewhat higher ^{14}C values than water from corresponding latitudes of the Pacific. This agrees with the assumption that deep sea water has its origin in the Weddel Sea, whereby the movement towards the east from the Weddel Sea to the South Pacific appears to be slower than the northward movement of the water in the Pacific Ocean. Measurements of the ^{14}C in surface water indicated that a considerable increase in ^{14}C was registered since 1958 as a result of nuclear tests. The increase is subject to strong regional variations and confirms the assumption that carbon-14 and also tritium absorption by the sea affects only a relatively shallow surface layer in the course of a few years, and that mixing of surface waters proceeds only relatively slowly. [VB 679/73 IE]

A History of Pigments and Dyestuffs

H. Kühn, Munich (Germany)

Analysis of inorganic pigments has proved useful as a means of dating paintings as well as for resolving the question of associating a painting with a particular period or specifying it as a later fake. A small pigment sample is removed under the stereomicroscope, an X-ray fine structure analysis is carried out, and its X-ray emission spectrum is recorded. Studies of this type carried out on paintings of fixed date have shown that certain pigments found only limited periodic and/or local application. Even though certain pigments have been employed over long periods of time, modern products can be distinguished quite characteristically from pigments of earlier origin by their particle size and fewer impurities.

White Pigments: The oldest is white lead ($2PbCO_3\cdot Pb(OH)_2$), which was produced synthetically since earliest times. Al-

though the same may be said of zinc white (ZnO), this pigment has only been used in artistic painting from about 1834; titanium oxide from about 1916.

Red Pigments: In early artistic painting, vermilion (HgS) was mostly used; for darker shades, red ochre (hematite and other red Fe-oxides) which was even previously used in cave drawings, was employed. Cadmium red (CdS–CdSe mixture) first appeared on the market after 1910. Red lead (Pb_3O_4), realgar (As_4S_4), and chrome red ($PbO \cdot PbCrO_4$), which is known since 1809, were but little used.

Yellow Pigments: Yellow ochre has also been known since the times of cave drawing. Auripigment (As_2S_3) was used in the 12th and 13th centuries, lead stannate ($PbSnO_3$) appeared from the 14th to the 17th centuries, and Naples yellow ($Pb_3(SbO_4)_2$) in the 18th century. Chrome yellow ($PbCrO_4$), zinc yellow ($ZnCrO_4$), barium yellow ($BaCrO_4$), and strontium yellow ($SrCrO_4$) appeared on the market around 1818; cadmium yellow (CaS) around 1845/50, and cobalt yellow ($K_3[Co(NO_2)_6]$) around 1860.

Green Pigments: Green-earth (glauconite, a weathered product, a silicate containing Ca, Mg, and Fe(II)) and malachite ($Cu(OH)_2 \cdot CuCO_3$) have been known since mediaeval times. The latter, just like verdigris ($Cu(OH)_2 \cdot Cu(CH_3COO)_2$, was used in artist's colors up to about 1800. The synthetic pigments "Scheele's green" ($Cu_3(AsO_3)_2$, introduced about 1778) and emerald green [$(Cu(CH_3COO) \cdot 3Cu(AsO_2)_2$; about 1814)], were soon displaced by chrome oxide green (Cr_2O_3; introduced about 1850) and chromium hydroxide green ($Cr_2O_3 \cdot H_2O$; about 1850) on account of their toxicity and instability. Combination of blue pigments and yellow pigments of the chromate type yielded chrome green (Prussian blue + chrome yellow) and zinc green (Prussian blue + zinc yellow). These colors therefore appeared simultaneously with the chrome pigments about 1818. Finally, cobalt green (a CoO/ZnO mixture) is to be found on paintings from after 1830.

Blue Pigments: Natural ultramarine (a Na-Al-silicate containing S) was used up to about 1830/40 and thereafter gave place to synthetic preparations. Differentiation is possible by means of microscopic examination of the grains. Azurite ($2\,CuCO_3 \cdot Cu(OH)_2$), frequently met with in mediaeval paintings, went out of use around the middle of the 19th century. Smalt (pulverized cobalt glass containing 2–7% CoO) is found in paintings dating from about the 16th century to the middle of the 19th century. As synthetic pigments, Prussian blue (from about 1750), cobalt blue ($CoO \cdot Al_2O_3$; from about 1810), and cerulean blue (Co–Sn-oxide; from about 1860) are of note. On the other hand, Bremen blue ($Cu(OH)_2$), manganese blue (a $BaSO_4/Ba_3(MnO_4)_2$ mixture), and tungsten blue (mixture of W-oxides) were rarely employed as artist's colors. Brown Pigments: Umber, like ochre, is an earth pigment(clay containing Fe and Mn). It is only encountered in paintings starting from the end of the 15th century; from the end of the 17th century and in the 18th century, Kassel brown (an earthy lignite) was also employed. From about 1900 onwards, the pigments Florentine brown ($Cu_2[Fe(CN)_6]$) and manganese brown ($Mn(OH)_3$) were known but were only used but little and for a short time.

Black Pigments: Lampblack, known since very early times, is still in use today, whereas the colors iron oxide black and manganese black (a $MnO_2/SiO_2/Fe_2O_3$ mixture), which were introduced around 1900, have hardly found acceptance in artistic painting.

Whereas inorganic pigments can be determined fairly easily, the identification of organic dyestuffs is substantially more difficult and requires the use of chromatographic and infrared spectroscopic methods. The artistic colors used in the main are redwood lake (in the Middle Ages), madder (17th–18th century), carmine (from the middle of the 16th century), Indian yellow (from the beginning of the 19th century), indigo (from about 1600), and mummy (about 1600–1900).

[GDCh, Section "History of Chemistry", Munich (Germany), September 13th, 1962]

[VB 655/59 IE]

Reactions of Silyl-Substituted Alkali Amides

U. Wannagat, Graz (Austria)

Metallation of $\rangle Si-NH-$ groups can be effected with LiC_3H_7, LiC_6H_5, Grignard reagents, K/liq. NH_3, $NaNH_2$/benzene, or Na/naphthalene/tetrahydrofuran. For alkoxysilicon compounds, only the last two reagents, and for hydrazinosilicons mainly the organolithium compounds are suitable. The $\rangle Si-N-Me$ group of any of the resultant alkali mono- and bis-silylamides or of the corresponding silylhydrazides, which are easily isolated and handled, reacts readily with halogenosilanes $XSiR_3$ to yield MeX and multiply silyl-substituted amines and hydrazines. In this way, new disilazanes $R_3SiNHSiR'_3$, disilyl anilines $C_6H_5N(SiR_3)_2$, trissilylamines $(RR'R''Si)_3N$, asymmetric bis-silyl- and tris-silylhydrazines $R_2NN(SiR_3)_2$ and $R_3SiNHN(SiR'_3)_2$, *N*-silylcyclotrisilazanes, and *N*-disilanyldisilazanes containing the group $Si-Si-NSi_2$ can be prepared (R = H, Halogen, *O*-alkyl, alkyl, alkenyl, aryl).

$NaN(SiR_3)_2$ reacts with non-metallic halides of other elements forming partly NaX and partly R_3SiX, so that complicated mixtures often result. The following products can be isolated, after reaction with I_2: $IN(SiR_3)_2$ (b. p. = 83 °C 16 mm; not absolutely pure); with S_2Cl_2: $[(R_3Si)_2NS-]_2$; with SCl_2: $[(R_3Si)_2N]_2S$ and $(R_3SiN)_2S$; with PCl_3: polymers of approximate composition $[(R_3Si)NPCl]_x$; with CCl_4, $CHCl_3$ or CH_2Cl_2: carbon and other products following a strongly exothermic reaction; with $COCl_2$: carbodiimides, $R_3SiN{=}C{=}NSiR_3$; with $SnCl_4$: mixtures of $(R_3Si)_2NSnCl_3$, $[(R_3Si)_2N]_2SnCl_2$, and $[R_3SiNSnCl_2]x$; with $HgBr_2$: in addition to Hg, a volatile, very labile HgNSi— compound.

On reacting with $NaN(SiR_3)_2$, compounds containing oxygen-non-metallic and a covalent element-oxygen double bond exchange =O for $-NSiR_3$ groups:

$$CO_2 \rightarrow C(NSiR_3)_2$$

$$\rangle CO \rightarrow \rangle C(NSiR_3)$$

$$SO_2 \rightarrow S(NSiR_3)_2$$

CS_2, on the other hand, reacts according to the equation:

$$2\,CS_2 + 4\,NaN(SiR_3)_2 \rightarrow 2\,N(SiR_3)_3 + S(SiR_3)_2 + Na_2S + 2\,NaSCN.$$

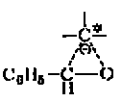
$C_6H_5NHNHSiR'_3$ can be metallated with LiC_6H_5, and after subsequent oxidation with Br_2, forms silylphenyldiazenes $C_6H_5N{=}N{-}SiR'_3$. These are deep blue liquids which can be distilled, but they are very sensitive towards moisture.

[Lecture, Technische Hochschule Aachen (Germany), November 6th, 1962]. [VB 660/63 IE]

Stereochemistry and Reaction Mechanism of the Isomerization of Anions Derived from Ethers

U. Schöllkopf, Heidelberg (Germany)

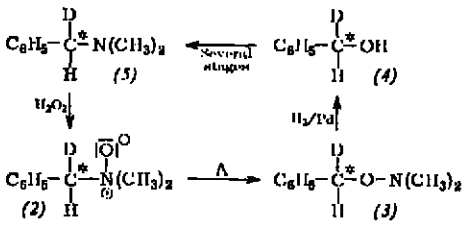
On isomerization, the optical activity of anions derived from optically active alkyl benzyl ethers is largely lost – a phenomenon which is contrary to an S_Ni mechanism involving the transition state *(1)*. Crossing experiments showed that at low



(1)

temperatures the rearrangement proceeds practically intramolecularly. Control experiments with deuterated model compounds proved that the racemization occured during the isomerization. The extent of the racemization depends upon the nature of the migrating group. A two stage elimination-addition mechanism is proposed and is able to explain the findings up to the present.

The stereochemistry of the rearrangement of amine oxides to hydroxylamine derivatives (Meisenheimer rearrangement) was also investigated. Here, the isomerization of optically active α-deutero benzyl - *N,N*-dimethylamine oxide *(2)* to optically active *O*-α-deutero benzyl-*N,N*-dimethylhydroxylamine *(3)* proved a suitable object for study. Compound *(2)* was obtained from the amine *(5)*, prepared by *Streitwieser* [1] from optically active α-deutero benzyl alcohol *(4)*. Compound *(3)* can be decomposed to give *(4)* without attack at the asymmetric centre.



Optical comparison of the original and recovered *(4)* showed that about 80% of the optical activity was lost. The optical rotations were measured with a photoelectric polarimeter (mean error ± 0.003 °). The deuterium atom is not exchanged for hydrogen during this cycle. These results favor a two-stage mechanism for the amine oxide rearrangement.

[GDCh-Ortsverband Marburg/Lahn (Germany),
November 9th, 1962] [VB 667/66 IE]

Chemistry of Metal Chlorides at High and Low Temperatures

Werner Fischer, Hannover (Germany)

Under certain conditions, the solubility of oxides in molten chlorides can be determined quite reliably, provided that the loss in weight which a sample of oxide undergoes during immersion in the chloride melt for a limited time can be measured. In $CaCl_2$ at 1000 °C, 0.07% by weight of MgO is dissolved. On adding small quantities of $MgCl_2$ or CaO to the $CaCl_2$, less MgO is dissolved. Within the limits of error the law of mass action is fulfilled:

$[Mg^{2+}]\,[O^{2-}] = 340$ (μmole/g)² at 1000 °C (*J. Gleisberg*)

In molten $CaCl_2$ at 1100 °C, less than 0.001% SiO_2 is dissolved (*H. Fauth*). At 900–1100 °C, in the presence of 0.5–8.4% by weight of CaO, $CaCl_2$ will dissolve cristobalite until a molar ratio of $CaO:SiO_2 = 3:2$ is reached but no further. Apparently, $Si_2O_7^{6-}$ ions are present in these melts, but no anions of higher silicic acids and no SiO_3^{2-} ions can exist (*J. Gleisberg*).

While the solubilities of individual rare earth chlorides in water at 0 °C differ from each other by only a few per cent, they decrease in the series from $LaCl_3$ to $ErCl_3$ in conc. hydrochloric acid at 0 °C by about two orders of magnitude (*H. Rohrer, J. Nier, T. Molaug, I. Dillo*, and *K. Trovaag*).

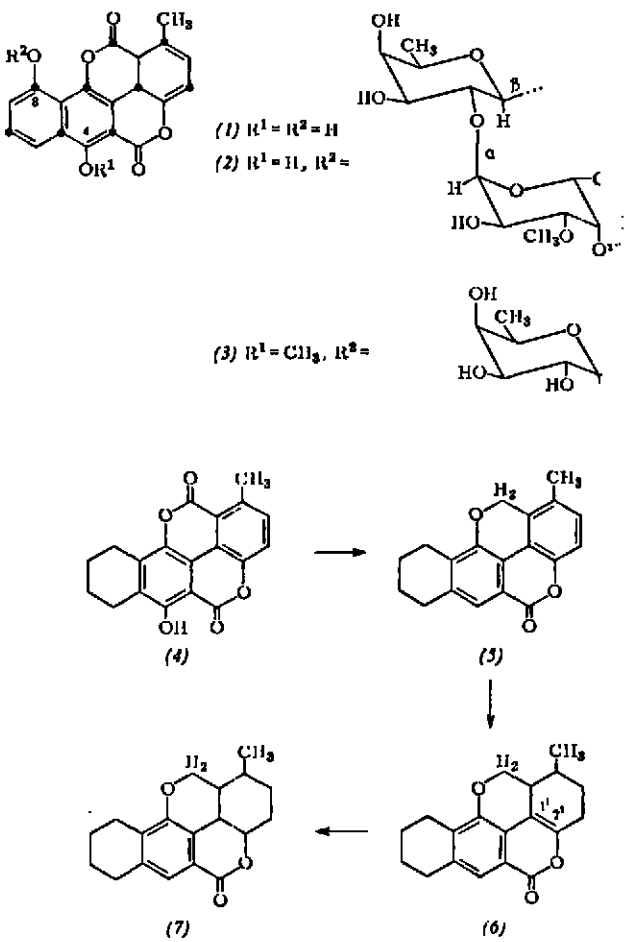
[GDCh-Ortsverband Aachen (Germany),
November 23rd, 1962] [VB 665/67 IE]

Chartreusin

Hans Schmid, Zurich (Switzerland)

According to *Sternbach, Kaiser*, and *Goldberg* [2], chartreusin (antibiotic X-465 A), $C_{32}H_{32}O_{14}$, which has been isolated from various strains of *Streptomyces* and which only shows antibiotic activity *in vitro*, is a glycoside with a disaccharide portion which consists of D-fucose and D-digitalose, and an aglycone portion which is derived from α-phenylnaphthalene or 2,3-benzofluorene. Experiments were reported that had led to the derivation of formula *(1)* for the aglycone of chartreusin [3]. The structures of some degradation products were supported by their NMR spectra. Since then, a series of products arising from vigorous catalytic hydrogenation of *(1)* [2] have been elucidated *[(4)–(7)]*. The reduction of a lactone group and the formation of an isocoumarin *(6)* are worthy of note.

It was demonstrated by degradation that the disaccharide portion of the antibiotic is attached through the 8-hydroxyl group of the aglycone. Thus, partial hydrolysis of the phenolic *O*-methyl ether of chartreusin gave *(3)*, and oxidation with periodic acid (uptake 1 HIO_4) followed by hydrolysis caused the appearance of methylglyoxal. From these experiments, from the observation that chartreusin methyl ether forms an acetonyl derivative, and on the basis of kinetic and immunochemical arguments which favor a pyranoid structure for the digitaloside portion, the constitution of chartreusin itself is deduced to be *(2)*. With the aid of the isorotation rules and NMR spectra, the stereochemistry of both the anomeric



centres of the two sugars were also derived; as a result of the anisotropic effect of the large aromatic aglycone portion, the NMR signals of the two relevant protons appear at abnormally small field strengths. Finally, it was shown that the aglycone of chartreusin *(1)* is biosynthetized entirely from acetic acid residues: the carbon atoms designated by • arise from the carboxyl groups, the others from the methyl groups of ten acetic acid residues.

[GDCh-Ortsverband Freiburg/Br. (Germany),
December 7th, 1962] [VB 673/69 IE]

[1] Thanks are due to Prof. *A. Streitwieser*, for valuable advice.

[2] *L. H. Sternbach, S. Kaiser*, and *M. W. Goldberg*, J. Amer. chem. Soc. *80*, 1639 (1958).

[3] *E. Simonitsch, W. Eisenhuth, O. A. Stamm*, and *H. Schmid*, Helv. chim. Acta *43*, 58 (1960).

Anions and Free Radicals of Acidic Hydrocarbons and their Aza-isologues

Richard Kuhn, Heidelberg (Germany)

Replacement of one fluorene residue in the "acidic" compound bis(biphenylene)propene by a 4 *H*-cyclopenta[d,e,f]-phenanthrene residue gives rise to the two isomers *(1)* (m.p. 252–254 °C, λ_{max_1} = 376 mμ) and *(2)* (m.p. 196–197 °C, λ_{max_1} = 346 mμ) (*F. A. Neugebauer*). Acids convert *(2)* into *(1)*. With bases, compounds *(1)* and *(2)* give the same red anion *(3)* (λ_{max_1} = 555 mμ), which on neutralisation yields *(1)* and *(2)* in an approximately 1:1 ratio [1].

(1) (Phe)C=CH–CH(Biph) $\overset{H^{\oplus}}{\underset{-H^{\oplus}}{\rightleftharpoons}}$ (Phe)CH–CH=C(Biph) *(2)*

(3) (Phe)C=CH–$\overset{\ominus}{C}$(Biph) ↕ (Phe)$\overset{\ominus}{C}$–CH=C(Biph) (Phe)C=CH–$\overset{\oplus}{C}$(Biph) ↕ (Phe)$\overset{\oplus}{C}$–CH=C(Biph) *(4)*

(5) (Phe)C=CH–C(CH_3)(Biph) (Phe)C(CH_3)–CH=C(Biph) *(6)*

(7) (Phe)C=CH–CH(Phe) (Phe)C=CH–$\overset{\oplus}{C}$(Phe) *(8)*

[1] Phe = 4,5-phenanthrylene, Biph = Biphenylene.

Methylation of *(1)* and *(2)* leads to *(5)* (m.p. 207–208 °C, λ_{max_1} = 380 mμ; yield *ca.* 56%) and *(6)* (m.p. 245–247 °C, λ_{max_1} = 348 mμ, yield *ca.* 28%) *via* the common anion *(3)*. Discharge of the anion *(3)* gives a mixture of dimeric hydrocarbons $C_{58}H_{34}$, which dissociate weakly in solution into the orange radicals *(4)* (λ_{max_1} = 515 mμ). Orange radicals *(8)*, which are nearly insensitive to oxygen, are formed by dissociation of a dimeric hydrocarbon $C_{62}H_{34}$ (m.p. 282–285 °C) which is obtained by discharge of the red anion (λ_{max_1} = 555 mμ) of *(7)* (m.p. 276–277 °C, λ_{max_1} = 376 mμ) (electron spin resonance spectra, *K. H. Hausser*).

The red compound *(9)* (m.p. 147–148 °C), which is obtained from fluorenone hydrazone and glutacondialdehyde, gives a

(Biph)C=N–NH–CH=CH–CH=CH–CH=N–N=C(Biph) *(9)*

green anion; its dissociation constants, however, are not greater than those of the aza-isologues previously described [2].

[GDCh-Ortsverband Berlin (Germany), November 26th, 1962] [VB 671/65 IE]

[2] *R. Kuhn*, Angew. Chem. internat. Edit. *1*, 602 (1962).

SELECTED ABSTRACTS

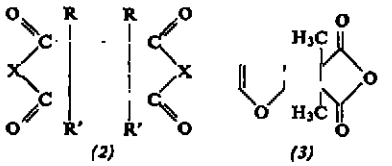
First prospects for successful chemotherapy of virus diseases have appeared. *R. Thiel* and *A. Wacker* have succeeded in curing a disease of the cornea of the eye, caused by a virus, by a method that had first been used by *H. E. Kaufman*. Drops of a 0.1% aqueous solution of the deoxyriboside of iodouracil were applied several times daily to the affected eye. The virus incorporates the "false" nucleoside into its nucleic acid in place of natural thymine. Its capacity for multiplication is thereby destroyed, and the virus becomes photosensitive, so that it can be killed by repeated irradiation of the eye with a special daylight lamp. / Klin. Monatsbl. Augenheilkunde augenärztl. Fortbild., No. 11 (1962) / –Hg. [Rd 413/115 IE]

The preparation of epoxides from substituted p-quinones and diazomethane is reported by *B. Eistert*, *H. Fink*, and *Annellese Müller*. The speed of reaction increases along the series tetraiodo-, tetrabromo-, tetrachloro-, and tetrafluoro-*p*-benzoquinone. Tetramethoxy-, tetra-acetoxy-, 2,6-dimethoxy-3,5 dibromo-, and 2,6-dimethoxy-*p*-benzoquinone also yield epoxides. 2,5-Dimethoxy-*p*-benzoquinone, in which the two methoxyl groups are involved in a vinylogous ester isomerism, does not react with diazomethane. Naphthaquinones which are substituted with chloro-, bromo-, or methoxyl groups in the 2- and 3-positions can also be converted into epoxides. Naphthaquinones which are substituted solely in the 2-position react *via* their double bond in the 2,3-position to form pyrazoline derivatives. Some of the epoxides thus obtained can be isomerized to aldehydes with boron trifluoride etherate, and hydrogenated to *p*-hydroxybenzyl alcohols. Boiling with 50% hydrochloric acid yields formaldehyde and the original quinone./Chem. Ber. *95*, 2403 (1962)/–W. [Rd 424/121 IE]

Zinc acetylides have been synthetized by *R. Nast*, *O. Künzel*, and *R. Müller*. The reaction between diphenylzinc and phenylacetylene (1:2) in ether gives an 80% yield of bis(phenylethynyl)zinc. In liquid NH_3, this forms a colorless, crystalline ammoniate, $Zn(C{\equiv}CC_6H_5)\cdot NH_3$. Reaction of $(C_6H_5)_2Zn$ and $C_6H_5C{\equiv}CH$ in a 1:1 molar ratio gives an approx. 80% yield of phenyl-phenylethynylzinc, $C_6H_5ZnC{\equiv}CC_6H_5$, m.p. 132.5–133.5 °C (decomp.). In ether, as in liquid NH_3, this compound decomposes into diphenylzinc and bis(phenylethynyl)zinc. Zinc amide suspended in liquid NH_3 reacts with acetylene to give the crystalline ammoniate of diethynylzinc, $Zn(C{\equiv}CH)_2\cdot NH_3$, which is very soluble in liquid NH_3 (non-electrolyte). The infrared spectra display the expected $\nu_{C\equiv C}$ frequencies. / Chem. Ber. *95*, 2155 (1962) / –Ma. [Rd 357/111 IE]

2-Benzyl-5,7-dinitrothiazolo[5,4-b]quinol-9-one, the first thiazoloquinolone with a functional group at C-9, was synthetized by *J. Dénes*, *M. Fărcăsan*, and *G. Ciudan*. 2-Chloro-3,5-dinitrobenzoic acid was condensed with 2-benzyl-5-aminothiazole in warm ethanol to give 3,5-dinitro-*N*-(2-benzyl-5-thiazolyl)anthranilic acid in 62% yield, m.p. 204 °C. Following the procedure for classical acridone syntheses, the ring was closed with phosphorus oxychloride to give the thiazoloquinolone in 58% yield, m.p. 238–239 °C. The substance forms a hydrochloride as well as silver, potassium, and piperidinium salts (m.p. 216–217 °C, decomp.). With methyl iodide, the silver salt gives the *N*-methyl derivative of the quinolone in 28% yield, m.p. 233–235 °C. / Chem. Ber. *95*, 2511 (1962) / W. [Rd 416/118 IE]

Cyclic dimers of maleic anhydride and its derivatives were synthetized by *G. O. Schenck*, *W. Hartmann*, *S.-V. Mannsfeld*, *W. Metzner*, and *C. H. Krauch* using a photoreaction with benzophenone as sensitizer (high pressure mercury arc, glass apparatus, argon; solvent: dioxan or benzene). The photochemical cycloaddition of these dienophiles, which does not proceed – or only very slowly – in the absence of benzophenone *(1)*, leads to symmetrical cyclobutadiene derivatives of type *(2)* (a: R = R′ = CH_3, X = O; b: R = CH_3, R′ = H or *vice versa*, X = O; c: R = R′ = H, X = O; d: R = R′ = CH_3, X = NH; e: R = R′ = H, X = N–C_6H_5; f: R = R′ = H, X = N–C_6H_{11}). Cyclobutadiindene (98.5%; m.p. 113 °C), the photodimer of indene, was obtained in particularly high quantum yield (0.9 based on the yield of benzopinacolone in isopropanol). The photosensitized addition of dimethylmaleic anhydride onto furan surprisingly takes place in the α,β-position and leads to 6,7-dimethyl-4-oxabicyclo-[3,2,0]hept-2-ene-6,7-dicarboxylic anhydride *(3)*, m.p. 153 °C. The adducts of dimethylmaleic anhydride onto ethylvinyl ether and of indene onto coumarin are obtained in an analogous manner. The dehydrogenating action of activated *(1)*,



(2) *(3)*

which normally leads to the formation of, for instance, the dioxan adduct of *(1)*, is suppressed in the presence of the above mentioned dienophiles. / Chem. Ber. *95*, 1642 (1962) / –Ku. [Rd 368/114 IE]

Die neuartigen polarographischen Methoden, ihr Prinzip und ihre Möglichkeiten (Novel Polarographic Methods, their Principles and Scope) by *Helmut Schmidt* and *M. v. Stackelberg*. Monographs to "Angewandte Chemie" and "Chemie-Ingenieur-Technik", No. 77. Verlag Chemie G.m.b.H., Weinheim/Bergstr. 1962. 1st Edition, 97 pp., bound DM 15.40 (about $4.00) [1].

Polarographic techniques have developed so much during the forty years since the invention of polarography that many new developments have escaped the notice not only of workers outside the field of polarography, but also of those who are concerned exclusively with so-called "classical" direct current polarography. Progress in polarographic techniques is not reported, however, in any of the existing text books on polarography. It is therefore to be welcomed that the author of one of the best text books on polarography, in collaboration with another author, has undertaken this task. This book provides chapters on stationary methods (classical, differential, derivative, and key polarography), on non-stationary methods (oscillographic methods and methods with superimposed alternating component, *i.e.* also square wave and pulse polarography), and constant current methods.

The most important merit of this book, in the reviewer's opinion, lies in its excellent style, which does not get lost in technical and constructional details but which describes the principles of the method, the basic circuit, and the original purpose of this technique or that apparatus. It can be said that this is one of the most useful text-books on polarography that have been published during the past few years. It ought to be translated into a language that would enable it to be read outside Central Europe.

J. Volke (Prague) [NB 924/29 IE]

Chromatographie en chimie organique et biologique (Chromatography in Organic and Biological Chemistry) in 2 Vols., edited by *E. Lederer*. Masson et Cie, Paris 1959/60. Vol. I. Généralités, applications en chimie organique (General principles, applications in organic chemistry). 671 pp., 164 illustrations, 144 tables, price NF 100.– (about $ 25.00); Vol. II. Applications en chimie biologique (Applications in biological chemistry). 876 pp., 98 illustrations, 251 tables, price NF 140.– (about $ 35.00).

This two-volume work, constituting volumes II and III in the series "Monographies de Chimie Organique" (supplementary to the well-known "Traité de Chimie Organique") is the first large-scale manual dealing with chromatographic procedures suitable for separation of organic compounds. The editor, *E. Lederer*, has been a leading contributor to the development of chromatography since its re-discovery and is co-author, with *M. Lederer*, of the well-known monograph "Chromatography" [2].

Twenty-eight French-speaking authors, including the editor, make their practical knowledge of the subject available in thirty-two contributions. The directions to authors for the style of their contributions were: 1. All reliable procedures to be described in such detail that they can be followed without reference to the original literature. 2. All other procedures to be cited briefly. 3. In the discussion of different procedures and their applications, always follow the order: adsorption, ion-exchange, partition, and at the same time always discuss column- and paper-chromatography separately. The fact that the 32 contributions have made a unified whole can be ascribed to the strict adherence to these guiding directions and the use throughout of precise and concise writing.

The work is divided into three parts. Part I (Volume I) contains four chapters on the theory and general basis of the various techniques of adsorption, ion-exchange, partition, and gas-chromatography. The concluding chapter covers the use of radio-isotopic techniques in chromatographic separations.

Part II (Volume I) covers applications of the various chromatographic techniques to organic chemistry and is divided according to classes of compounds (carbohydrates, alcohols, acids, amines, alkaloids, *etc.*). This part concludes with an outstanding contribution on the separation of stereoisomers (geometric isomers, diastereoisomers, resolution of racemates). Volume II contains the third and largest part (Part III), on the chromatography of naturally occurring compounds. Here, also, the material is divided according to the class of substance (sugars, amino acids, peptides, steroids, vitamins, hormones, antibiotics, *etc.*). Not only the chemist, but also the biologist, the microbiologist, and the physiologist can draw rich profit from the material presented here. It is regrettable that so brief reference is made to thin-layer chromatography, which has recently found more and more frequent application. It receives only a single mention. The reason may be that its importance was not so well recognized at the time of the literature deadline for the work – the first volume appeared in 1959 – as it is today.

More than in other separation techniques, success in chromatography depends on the details of the procedure, *i.e.* the type and activity of the adsorbent, the type of ion-exchange resin, the eluting capacity of the solvents, and the partition coefficient of the solvent system used must be optimal for the particular separation problem. Hence there are innumerable data in the literature on new and novel variations of experimental conditions, and it is a wearisome task to select the best for any particular case. The great merit of *E. Lederer*'s handbook is that this task will henceforth be much lighter, now that specialists have gathered and critically examined the vast amount of original material and have so presented proved methods that it is possible to work without reference to the original literature. As an excellent collection, with numerous illustrations, tables of R_F values, details of solvent systems, and reagents for the detection of colorless compounds, together with more than 6200 literature references, these volumes will quickly become an indispensible guide in all chromatographic work, even for those little acquainted with the French language.

H. Brockmann [NB 907/28 IE]

[1] An English edition of this monograph will be published shortly by Academic Press Inc., New York and London.

[2] Cf. Angew. Chem. *66*, 492 (1954); *69*, 520 (1957).

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Recent Developments in Organotin Chemistry

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CHEMISCHES INSTITUT DER UNIVERSITÄT GIESSEN (GERMANY)

RESULTS FROM WORK DONE WITH ASSISTANCE OF G. BURKHARDT, E. HEYMANN, F. KLEINER, K. KÖNIG, H. NIERMANN, J. PEDAIN, R. SCHICK, R. SOMMER, AND H. WELLER

New synthetic methods developed in the field of organotin compounds since 1959 are reviewed. The use of alkyl aluminum compounds brings an advance in the preparation of tetraalkyltin derivatives, alkyltin halides, and alkyltin hydrides. Organotin hydrides offer new possibilities for the production of monomeric and polymeric organotin compounds. Diethyltin and diphenyltin, which are obtained by catalytic dehydrogenation of the respective dialkyltin dihydrides, are cyclic compounds. – The literature since 1959 is reviewed.

1. Introduction

As in organometallic chemistry as a whole, great progress has been made over the last eight years in the field of organotin compounds. New synthetic methods have been developed, and it is now possible to prepare alkyltin compounds containing almost any desired substituent at practically any position in the molecule. This survey covers the progress made since 1959, earlier work having been treated in two previous reviews [1,2].

The development has been furthered in part by the keen interest of industry. Organotin compounds are used as stabilizers for halogen-containing plastics and polyamides [3], as biocides [4], as preservatives for wood, paints, and leather, in the manufacture of paper, in plant protection [5], and in preventing fouling of ships [6]. Tin alkyls have also been tested as activators and polymerization catalysts [6].

Organotin compounds with short-chain alkyl residues can have toxic effects [7–9]. Cleanliness and caution are therefore indicated when working with tin alkyls.

2. Preparation of Tetraalkyltin Compounds

Tetraalkyltin compounds are of particular importance as intermediates. Until recently, they were obtained almost exclusively by two methods [1,2]; *via* Grignard syntheses (X = halogen):

$$4\,RMgX + SnX_4 \rightarrow R_4Sn + 4\,MgX_2$$

or by treating tin alloys with alkyl halides:

$$Sn + 4\,Na + 4\,RX \rightarrow R_4Sn + 4\,NaX$$

Variations in both procedures are known, *e.g.*, using alkyl lithium compounds, different tin alloys or other

[*] From lectures given in Frankfurt/Main, Gießen, Darmstadt, Clausthal-Zellerfeld, Leverkusen, Aachen, Munich, Mülheim-Ruhr, Köln (Germany), and Utrecht (The Netherlands).

[1] *G. J. M. van der Kerk, J. G. A. Luijten,* and *J. G. Noltes,* Angew. Chem. *70,* 298 (1958).

[2] *R. K. Ingham, S. D. Rosenberg,* and *H. Gilman,* Chem. Reviews *60,* 459 (1960).

[3] French Pat. 1253028 (March 31st, 1960), Union Carbide Corp., inventors *C. F. Horn* and *H. Vineyard.*

[4] *G. J. M. van der Kerk, J. G. A. Luijten, J. C. van Egmond,* and *J. G. Noltes,* Chimia *16,* 36 (1962), further references are given here.

[5] *R. J. Zedler,* Zinn u. seine Verwend. *53,* 7 (1961).

[6] *W. A. Johnson,* Zinn u. seine Verwend. *54,* 5 (1962).

[7] *H. B. Stoner, J. M. Barnes,* and *J. I. Duff,* Brit. J. Pharmacol. Chemotherapy *10,* 16 (1955).

[8] *J. M. Barnes* and *H. B. Stoner,* Pharmacol. Rev. *11,* 211 (1959), further references are given here.

[9] *G. Tauberger* and *O. R. Klimmer,* Arch. exp. Pathol. u. Pharmakol. *242,* 370 (1961).

reactants [10,11]. Both these methods, however, do not yield pure tetraalkyltin derivatives. Even when a considerable excess of the relatively expensive alkylating agents is used, the product always contains the less highly alkylated species R_3SnX and R_2SnX_2 as impurities which are sometimes hard to separate [12].

The work of *Ziegler* and co-workers [13] has made alkyl aluminum compounds readily available. It therefore became worthwhile to investigate their use as substitutes for the alkylating agents mentioned above in the preparation of tin alkyls, according to the equation

$$4\ R_3Al + 3\ SnX_4 \rightarrow 3\ R_4Sn + 4\ AlX_3$$ [14].

The first to report such reactions were *Zakharkin* and *Okhlobystin* [15]. However, the results that they and others [16–18] have obtained are far from satisfactory: Some of the alkyl groups always remained attached to the aluminum, and several degrees of alkylation of the tin were obtained simultaneously. The method seemed to offer more promise for the preparation of trialkyl and dialkyltin halides, but in this case, too, equilibrium mixtures were obtained [4,15–17].

If, for example, triethylaluminum and stannic chloride are allowed to react together in a molar ratio of 4:3, at equilibrium 30 % of the ethyl groups remain attached to the aluminum, as determined by measuring the evolution of ethane on alcoholysis. The tin is distributed as follows: 8 % as $SnCl_4$, 8 % as diethyltin dichloride, 74 % as triethyltin chloride, and only 10 % as tetraethyltin [18, 21]. In this reaction, *Köster* [14] obtained the novel complexes $(C_2H_5)_3SnCl \cdot AlCl_3$ and $(C_2H_5)_2SnCl_2 \cdot AlCl_3$, which obviously hinder further alkylation of the tin. These complexes form well-defined crystals. Further compounds of this nature have been found and investigated [23]. Depending on the solvent, the conductivity of the solutions varies from good to excellent. Simple ions like R_3Sn^+ and $AlCl_4^-$, however, are not present: the molecular weights in solution are higher than 3000 in the case of compounds $R_3SnCl \cdot AlCl_3$. There are chains present, probably with pentacoordinated tin atoms [23]. Such a pentacoordination is known from other trialkyltin compounds (see Chapter 4).

The preparation of tin tetraalkyls becomes surprisingly simple if a powerful complexing agent is used to trap the aluminum halide expected as by-product. A quantitative yield of tetraalkyltin can then be obtained without the use of a significant excess of aluminum alkyl. Alkali metal halides, ethers, and tertiary amines are the most suitable complexing agents:

$$4\ R_3Al + 4\ NaCl + 3\ SnCl_4 \rightarrow 3\ R_4Sn + 4\ NaAlCl_4$$ [19, 20, 91]

$$4\ R_3Al + 4\ R'_2O + 3\ SnCl_4 \rightarrow 3\ R_4Sn + 4\ Cl_3Al \cdot OR'_2$$ [20, 21]

$$4\ R_3Al + 4\ NR'_3 + 3\ SnCl_4 \rightarrow 3\ R_4Sn + 4\ Cl_3Al \cdot NR'_3$$ [20, 21]

These reactions appear to be promising on an industrial scale, too. Sodium fluoride has also been mentioned as a complexing agent and $NaAlR_4$ as an alkylating agent [22, 22a].

The yields are excellent. The alkyl residues can be ethyl, n-butyl, isobutyl, n-octyl [19–21], or phenyl [23a]. The more volatile alkyltin compounds can be distilled off *in vacuo*. In the case of ether complexes, partial or complete separation of the reaction mixture into two phases usually occurs, depending on the alkyl residue; the heavy $AlCl_3$ complex is drained off. Only rarely must it be hydrolyzed [20, 21]. The tetraalkyltin compounds are obtained in the pure state.

Tin alkoxides have been alkylated with Grignard reagents [24] and with aluminum alkyls [20]:

$$4\ R_3Al + 3\ Sn(OR')_4 \rightarrow 3\ R_4Sn + 4\ Al(OR')_3.$$

Since aluminum alkoxides are very strongly associated, complexing agents are not needed.

With regard to cyclic tetraalkyltin compounds, besides the derivatives of stannacyclohexane [25], stannacycloheptane [26] and stannacyclopentadiene [27,28] have now become known.

The C–Sn bonds in tin tetraalkyls are very stable. Their cleavage by bromine [25, 29, 29a, 30], *N*-bromosuccinimide [30a], alkyl halides and ultraviolet irradiation [30b], peroxides [30c],

[10] *C. R. Dillard* et al., J. Amer. chem. Soc. *80*, 3607 (1958).

[11] Belg. Pat. 600465 (Febr. 22nd, 1961), Dtsch. Advance Prod., inventors *I. Hechenbleikner* and *K. R. Molt*; Brit. Pat. 854776 (Aug. 12th, 1959), Ass. Lead Manuf., inventor *F. B. Lewis*; Brit. Pat. 813479 (Nov. 26th, 1957), Metal and Thermit Corp., inventors *S. D. Rosenberg* and *A. J. Gibbons*; Brit. Pat. 825039 (May 4th, 1956), Metal and Thermit Corp., inventor *H. E. Ramsden*; French. Pat. 1246453 (Jan. 5th, 1960), Ethyl Corp., inventor *G. C. Robinson*; *I. Katsumara*, J. Chem. Soc. Japan *83*, 724 (1962).

[12] For example US.-Pat. 2718522 (Sept. 2nd, 1955) and German Published Patent Application 1045402 (Nov. 30th, 1956), Metal and Thermit Corp., inventor *C. R. Gloskey*; Belg. Pat. 607414 (Aug. 22nd, 1961), Metal and Thermit Corp., inventor *J. E. Santo*.

[13] *K. Ziegler, H. G. Gellert, H. Lehmkuhl, W. Pfohl*, and *K. Zosel*, Angew. Chem. *67*, 424 (1955); LiebigsAnn. Chem. *629*, 1 (1960).

[14] For example *R. Köster*, personal communication. See also *H. Zeiss*: Organometallic Chemistry. Reinhold Publ. Corp., New York 1960, p. 247.

[15] *L. I. Zakharkin* and *O. Yu. Okhlobystin*, Dokl. Akad. Nauk SSSR *116*, 236 (1957); Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1959*, 1942.

[16] *W. K. Johnson*, J. org. Chemistry *25*, 2253 (1960).

[17] *J. C. van Egmond, M. J. Janssen, J. G. A. Luijten, G. J. M. van der Kerk*, and *G. M. van der Want*, J. appl. Chem. *12*, 17 (1962).

[18] *W. P. Neumann*, unpublished.

[19] German Published Patent Application 1048275 (July 14th, 1956), Kali-Chemie AG., inventors *H. Jenkner* u. *H. W. Schmidt*.

[20] *W. P. Neumann*, Liebigs Ann. Chem. *653*, 157 (1962).

[21] Belg. Pat. 590209 and 590210 (April 27th, 1960), inventors *K. Ziegler* and *W. P. Neumann*.

[22] German Published Patent Application 1054454 (Jan. 17th, 1958), Badische Anilin- und Sodafabrik, inventor *H. Müller*.

[22a] French Pat. 1270914 (Oct. 14th, 1960), Kali-Chemie AG., inventor *H. Jenkner*.

[23] *W. P. Neumann* and *R. Schick*, unpublished. *R. Schick*, diploma thesis, Universität Gießen, 1962.

[23a] *D. Wittenberg*, Liebigs Ann. Chem. *654*, 23 (1962); German Published Patent Application 1124947 (Dec. 10th, 1960), Badische Anilin- u. Sodafabrik, inventor *D. Wittenberg*.

[24] *J. Cl. Maire*, C. R. hebd. Séances Acad. Sci. *249*, 1359 (1959).

[25] *E. Krause* and *A. v. Grosse*: Die Chemie der metallorganischen Verbindungen. Borntraeger, Berlin 1937; see also *G. Grüttner, E. Krause* and *M. Wiernik*, Ber. dtsch. chem. Ges. *48*, 1413 (1915); *50*, 1549 (1917); *R. Polster*, Liebigs Ann. Chem. *654*, 20 (1962).

[26] *H. G. Kuivila* and *O. F. Beumel Jr.*, J. Amer. chem. Soc. *80*, 3250 (1958).

[27] *F. C. Leavitt, T. A. Manuel*, and *F. Johnson*, J. Amer. chem. Soc. *81*, 3163 (1959); *E. H. Braye, W. Hübel*, and *J. Caplier*, ibid. *83*, 4406 (1961).

[28] *R. Gelius*, Angew. Chem. *72*, 322 (1960).

[29] *S. D. Rosenberg, E. Debreczeni*, and *E. L. Weinberg*, J. Amer. chem. Soc. *81*, 972 (1959).

[29a] *Z. M. Manulkin*, Zh. obshch. Khim. *14*, 1047 (1944).

[30] *G. J. M. van der Kerk* and *J. G. Noltes*, J. appl. Chem. 9, 179 (1959).

[30a] *E. J. Kupchik* and *T. Lanigan*, J. org. Chemistry *27*, 3661 (1962).

[30b] *G. A. Razuvaev, N. S. Vjazankin, E. N. Gladysev*, and *J. A. Borodavko*, Zh. obshch. Khim. *32*, 2154 (1962).

[30c] *G. A. Razuvaev, N. S. Vjazankin*, and *O. S. Dyaschkovskaya*, Zh. obshch. Khim. *32*, 2161 (1962).

salts [30d], sulfur [30e], or by acids with dissociation constants from 10^{-1} to 10^{-10} [31], the stability of the tetraphenyl derivatives [32], and the formation and stability of tetraalkyltin compounds containing bulky aromatic groups [33] have been studied.

3. Preparation of Organotin Halides

The organotin halides R_3SnX, R_2SnX_2, and $RSnX_3$ are prepared almost exclusively above 180 °C using the comproportionation method according to *Kozeschkow* [34].

$$3\ R_4Sn + SnCl_4 \rightarrow 4\ R_3SnCl$$
$$R_4Sn + SnCl_4 \rightarrow 2\ R_2SnCl_2$$
$$R_4Sn + 3\ SnCl_4 \rightarrow 4\ RSnCl_3$$

Whereas in the first two reactions high yields are obtained with both aromatic and aliphatic organotin compounds [2, 34–36], so far the third has been restricted to aromatic [34, 36] and vinyl [37] compounds. Aliphatic alkyltin trihalides are usually obtained *via* alkylstannic acids [2]. A better procedure is afforded by the following reaction, which occurs at temperatures as low as 0 to 20 °C [38]:

$$(C_4H_9)_4Sn + SnCl_4 \rightarrow (C_4H_9)_3SnCl + C_4H_9SnCl_3.$$

The above reaction is not an isolated case; it is the first stage in all *Kozeschkow* comproportionations [39]. At the high temperature of the process however, the alkyltin trichloride stage is passed through so rapidly that, until recently, it escaped detection. The formation of the intermediate compounds can be followed by gas chromatography (Fig. 1) during the synthesis of diethyltin dichloride from equimolar amounts of tetraethyltin and stannic chloride. The reaction leading to ethyltin trichloride and triethyltin chloride is completed as soon as the reactants are mixed together; it is only thereafter that diethyltin dichloride begins to form slowly. The trihalide is also produced from trialkyltin chloride and stannic chloride [39]:

$$R_3SnCl + SnCl_4 \rightarrow R_2SnCl_2 + RSnCl_3.$$

If the two reactions are combined, then two-thirds of the tin is obtained as the alkyltin trihalide and one-third as easily separable dialkyltin dichloride, all in one step.

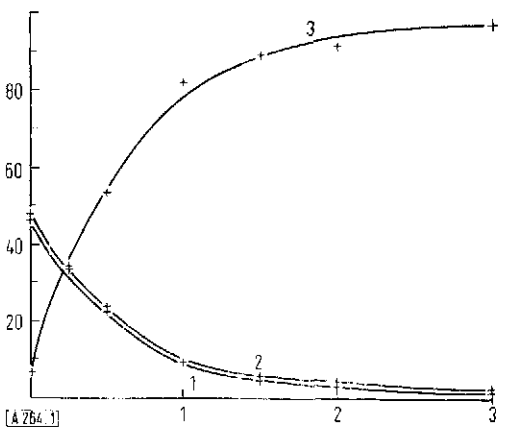


Fig. 1. Course of the reaction [39]

$$(C_2H_5)_4Sn + SnCl_4 \rightarrow (C_2H_5)_3SnCl + C_2H_5SnCl_3 \xrightarrow{200\ °C} 2\ (C_2H_5)_2SnCl_2$$

Curve 1: Concentration of $(C_2H_5)_3SnCl$
Curve 2: Concentration of $C_2H_5SnCl_3$
Curve 3: Concentration of $(C_2H_5)_2SnCl_2$
The concentrations were determined by gas chromatography [39].
Ordinate: Concentration [mole-%]
Abscissa: Time [hr]

Any excess $SnCl_4$ does not enter into the reaction.

$$R_4Sn + 2\ SnCl_4 \rightarrow R_2SnCl_2 + 2\ RSnCl_3$$

Alkyltin halides may also be prepared by treating tin with alkyl halides:

$$Sn + 2\ RX \rightarrow R_2SnX_2.$$

This type of reaction, which affords high yields with silicon, was long restricted to the methyl compound for tin [40,41]. Recently, however, tin has been found to react with alkyl halides in which the halogen is especially mobile and which do not lose HCl to give an olefin.

Thus, diallyltin dibromide is formed in 82 % yield when powdered tin and allyl bromide react in boiling toluene, using $HgCl_2$ and pyridine (or other bases) as catalysts [42]. The reaction also succeeds with crotyl bromide. Dibenzyltin dichloride has been prepared in 88 % yield in boiling toluene, and yields of tribenzyltin chloride as high as 94 % have been obtained in boiling water or butanol [43]:

$$3\ C_6H_5CH_2Cl + 2\ Sn \rightarrow (C_6H_5CH_2)_3SnCl + SnCl_2$$

Similar results were obtained with certain substituted benzyl chlorides [44] and with other alkyl halides [45]. Cumyl chloride reacts with tin dust even at room temperature to form both R_2SnCl_2 and R_3SnCl [46]. Dibutyltin dibromide can be obtained from n-butyl bromide by irradiation with γ-rays [47]. Dialkyltin dichloride reacts with an alkyl chloride

[30d] *H. H. Anderson*, Inorg. Chemistry *1*, 647 (1962).

[30e] *M. Schmidt, H.-J. Dersin*, and *H. Schumann*, Chem. Ber. *95*, 1428 (1962).

[31] *R. Sasin* and *G. S. Sasin*, J. org. Chemistry *20*, 770 (1955); *G. S. Sasin, A. L. Borror*, and *R. Sasin*, ibid. *23*, 1366 (1958).

[32] *L. M. Nazarova*, Zh. obshch. Khim. *31*, 1119 (1961).

[33] *G. Bähr* and *R. Gelius*, Chem. Ber. *91*, 812, 818 (1958).

[34] *K. A. Kozeschkow*, Ber. dtsch. chem. Ges. *62*, 996 (1929) *66*, 1661 (1933).

[35] German Published Patent Application 1100630 (Oct. 1st 1959), Farbwerke Hoechst A.-G., inventors *E. Reindl* u. *H. Gelbert*.

[36] *H. Zimmer* and *H. W. Sparmann*, Chem. Ber. *87*, 645 (1954); *H. Gilman* and *L. A. Gist Jr.*, J. org. Chemistry *22*, 368 (1957).

[37] *D. Seyferth* and *F. G. A. Stone*, J. Amer. chem. Soc. *79*, 515 (1957); *S. D. Rosenberg* and *A. J. Gibbons Jr.*, ibid. *79*, 2138 (1957).

[38] Brit. Pat. 739883 (Nov. 2nd, 1955), Metal and Thermit Corp.

[39] *W. P. Neumann* u. *G. Burkhardt*, Liebigs Ann. Chem. (1963), in the press; *G. Burkhardt*, diploma thesis, Universität Gießen, 1961.

[40] German Published Patent Application 1046052 (Aug. 27th, 1953), Metal and Thermit Corp., inventors *E. L. Weinberg* and *E. G. Rochow*.

[41] German Published Patent Application 1050336 (Febr. 22nd, 1958), Th. Goldschmidt A.-G., inventors *R. Irmscher, W. Knöpke* and *H. Kunze*.

[42] *K. Sisido* and *Y. Takeda*, J. org. Chemistry *26*, 2301 (1961).

[43] *K. Sisido, Y. Takeda* and *Z. Kinugawa*, J. Amer. chem. Soc. *83*, 538 (1961).

[44] German Published Patent Application 1069626 (Oct. 2nd, 1958), German Published Patent Application 1119863 (March 25th, 1960), Deutsche Advance Prod. GmbH., inventors *A. Hartmann* and *D. Pirck*.

[45] Russ. Pat. 137519 (Aug. 24th, 1960), inventors *L. W. Laine* et al.; *H. Matsuso, H. Tairguki* and *S. Matsudo*, J. chem. Soc. Japan *35*, 208 (1962), ibid., ind. chem. Sect. *64*, 541 (1961).

[46] *O. Danek*, Collect. czechoslov. chem. Commun. *26*, 2035 (1961).

[47] *L. V. Abramova, Y. Y. Sheverdina*, and *V. A. Kocheshkov*, Dokl. Akad. Nauk SSSR *123*, 681 (1958); Russ. Pat. 136313 (July 30th, 1960), inventors *L. W. Abramova* et al.

in the presence of aluminum chloride to give the trialkyltin chloride [48]. Methyltin chlorides are also formed from tin(II) oxide and methyl chloride at 250–350 °C [48a].

Finally, stannic halides, particularly the chloride, can be partially alkylated, *e.g.*, with aluminum alkyls [16,49]. *Van der Kerk* et al. studied the formation of isobutyltin chlorides, albeit in a low-boiling, halogenated solvent, and discussed the concept of "alkylation potentials" [4,17].

Here, as in the synthesis of tin tetraalkyls, complex formation between tin derivatives and aluminum derivatives prevents the reaction from going to completion [18,20,21]. When equimolar quantities of triethylaluminum and stannic chloride are used, the equilibrium composition is as follows: 25 % of the ethyl groups remain attached to the aluminum, 1.5 % of the tin is converted into tetraethyltin, 25 % are converted into diethyltin dichloride, 17.5 % remain unchanged as $SnCl_4$, and only 56 % are converted into triethyltin chloride. The reaction

$$2\ AlR_3 + 3\ SnCl_4 \rightarrow 3\ R_2SnCl_2 + 2\ AlCl_3 \quad (R = C_2H_5)$$

does not proceed smoothly either. In this case, 7 % of the ethyl groups remain attached to the aluminum, 26 % of the tin remain unchanged as $SnCl_4$, 38 % are converted into triethyltin chloride, and only 36 % form diethyltin dichloride [18,21].

Much better results are obtained if the complexing agents for aluminum trichloride already mentioned are added. No ethyl groups remain on the aluminum, and the alkyltin chloride can be isolated in good yield. In an analogous manner, partial alkylation of stannic chloride has made it possible to prepare a large number of alkyltin halides of the types R_3SnX and R_2SnX_2 (X = chlorine, bromine, or iodine) in a single step[20,21,23a, 50]. Other organoaluminum compounds, especially alkylaluminum halides, may be used instead of aluminum trialkyls. Dialkylaluminum alkoxides are apparently suitable for the preparation of alkyltin trihalides [20,21].

4. Syntheses Using Organotin Halides

Currently, almost all important organotin compounds are prepared from the appropriate halides [1,2]. This is especially true of alkyltin derivatives in which the organic residues contain functional groups. These compounds can also be obtained from organotin hydrides (see Sect. 6).

New syntheses of and with organotin halides have become known [50a]. *Tamborski* and *Soloski* [51] synthetized the first organotin-magnesium compound

$$2\ (C_6H_5)_3SnCl + 2\ Mg \xrightarrow[C_2H_5Br]{THF} [(C_6H_5)_3Sn]_2Mg + MgCl_2$$

(THF = tetrahydrofuran)

which on hydrolysis, for example, is said to give 82 % triphenyltin hydride. The equilibrium

$$R_3SnLi \rightleftharpoons R_2Sn + RLi$$

has been proposed for trialkyl- or triaryltin-lithium compounds [51,51a]. This equilibrium, however, does not occur in the case of triphenyltin-lithium [52,53], which reacts smoothly with sulfur, selenium and tellurium [51b]. Tributyltin-lithium, on the other hand, gives reactions which can only be explained by postulating an alkyllithium compound as an intermediate [53] a phenomenon which had already been encountered with the ethyl compound [54].

Reactions with sodium chlorophenoxides [55] have been studied, as well as the preparation of organometallic peroxy compounds [56] and endoperoxides [57]. The trialkyltin halides are easily converted into the alkoxy derivatives. These react smoothly with ketene to yield compounds of the type R_3SnCH_2COOR' [58], and with enol acetates at room temperature to give α-trialkylstannyl ketones in 95 % yield [59]:

$$R_3SnOCH_3 + H_2C{=}C(OCO{-}CH_3){-}CH_3 \rightarrow R_3Sn{-}CH_2{-}CO{-}CH_3 + H_3CCOOCH_3$$

The hydrolysis and alcoholysis of alkyltin halides [60,61] and the chemistry of the resulting stannoxanes $R_3Sn{-}O{-}SnR_3$ [62–64] or dialkyltin oxides [64a] have been investigated. Tributyltin oxide ("TBTO"), which has become industrially important, belongs to this group [65]. It is worth mentioning that the products of partial hydrolysis of several dialkyltin dihalides, which until recently were described by the empirical formula $R_4Sn_2X_2$ [66], are actually cyclic dimers or trimers of the respective stannoxanes [67,68].

[48] *G. A. Razuvaev, N. S. Vyazankin, O. S. D'yachkovskaya, J. G. Kiseleva,* and *Yu. J. Dergunov,* Zh. obshch. Khim. *31*, 4056 (1960).

[48a] *K. A. Andrianov, T. V. Vasileva* et al., Zh. obshch. Khim. *32*, 2307 (1962).

[49] *L. I. Zakharkin* and *O. Yu. Okhlobystin,* Zh. obshch. Khim. *31*, 3662 (1961).

[50] Brit. Pat. 802796 (Oct. 8th, 1958), US.-Pat. 3027393 (July 11th, 1957), Kali-Chemie A.-G., inventors *H. Jenkner* and *H. W. Schmidt.*

[50a] For example *D. L. Alleston* and *A. G. Davies,* J. chem. Soc. (London), 2050 (1962); *I. R. Beattie* and *G. J. Leigh,* J. inorg. nuclear Chem. *23*, 55 (1961).

[51] *C. Tamborski* and *E. J. Soloski,* J. Amer. chem. Soc. *83*, 3734 (1961); J. org. Chemistry *27*, 619 (1962).

[51a] *H. Gilman, O. L. Marrs, W. J. Trepka,* and *J. W. Diehl,* J. org. Chemistry *27*, 1260 (1962).

[51b] *H. Schumann, K. F. Thom,* and *M. Schmidt,* Angew. Chem. *75*, 138 (1963).

[52] *H. Gilman* and *S. D. Rosenberg,* J. org. Chemistry *18*, 1554 (1953).

[53] *D. Blake, G. E. Coates,* and *J. M. Tate,* J. chem. Soc. (London) 618 (1961).

[54] *H. Gilman* and *S. D. Rosenberg,* J. Amer. chem. Soc. *75*, 2507 (1953).

[55] *J. D'Ans* and *H. Gold,* Chem. Ber. *92*, 3076 (1959).

[56] *A. Rieche* and *T. Bertz,* Angew. Chem. *70*, 507 (1958); *W. A. Susumov* and *T. G. Brilkina,* Dokl. Akad. Nauk SSSR *141*, 1391 (1961); *N. S. Vyazankin, G. A. Rasuvaev* et al., ibid. *143*, 1348 (1962); *D. L. Alleston* and *A. G. Davies,* J. chem. Soc. (London) 2465 (1962).

[57] *G. O. Schenck, E. Koerner von Gustorf,* and *H. Köller,* Angew. Chem. *73*, 707 (1961).

[58] *I. F. Lutsenko* and *S. V. Ponomarev,* Zh. obshch. Khim. *31*, 2025 (1961).

[59] *A. N. Nesmeyanov, I. F. Lutsenko,* and *S. V. Ponomarev,* Dokl. Akad. Nauk SSSR *124*, 1073 (1959).

[60] *R. H. Prince,* J. chem. Soc. (London) 1783 (1959).

[61] *R. Okawara* and *E. G. Rochow,* J. Amer. chem. Soc. *82*, 3285 (1960).

[62] *R. Okawara,* Proc. chem. Soc. (London) 383 (1961); *R. Okawara* and *K. Sugita,* J. Amer. chem. Soc. *83*, 4480 (1961); *R. Okawara, D. G. White, K. Fujitani,* and *H. Sato, ibid.* 1342.

[63] *H. Schmidbauer* and *M. Schmidt,* J. Amer. chem. Soc. *83*, 2963 (1961).

[64] *S. M. Shivuchin, E. D. Dudikova,* and *V. V. Kireev,* Zh. obshch. Khim. *31*, 3106 (1961); *32*, 3059 (1962).

[64a] *W. T. Reichle,* Inorg. Chem. *1*, 650 (1962).

[65] German Published Patent Application 1089757 (Aug. 21st. 1959), Farbwerke Hoechst A.-G., inventor *H. Gelbert; C. R. Gloskey,* Chem. Engng. Progr. *58*, 71 (1962).

[66] *H. O. Johnson* and *H. E. Fritz,* J. org. Chemistry *19*, 74 (1954); J. Amer. chem. Soc. *77*, 5857 (1955).

[67] *A. J. Gibbons, A. K. Sawyer,* and *A. Ross,* J. org. Chemistry *26*, 2304 (1961).

[68] *D. L. Alleston* and *A. G. Davies,* Chem. and Ind. 949 (1961); *D. L. Alleston, A. G. Davies,* and *B. N. Figgis,* Proc. chem. Soc. (London) 457 (1961).

Wiberg and *Rieger* [69] have prepared substituted organotin amides from alkyltin chlorides and alkali metal compounds of secondary amines, *e.g.*,

$$R_3SnCl + LiNR'_2 \rightarrow R_3Sn{-}NR'_2 + LiCl.$$

The method has been modified [70,70a] and extended to a number of cyclic secondary amines, *e.g.*, imidazole [70]. The same products may be obtained by treating alkyltin oxides or hydroxides (prepared from the halides) with free secondary amines; the water liberated is removed by azeotropic distillation [70]. An additional, new synthetic method is described in Sect. 6. The organotin amides are mostly hydrolyzed by water. They have become rather interesting, since some stable trialkyl derivatives with pentacoordinated tin atoms have been found [70,70b]. This surprising structure principle has meanwhile been shown to exist also in trialkylacylates [70c], tetrachloroaluminates (see Sect. 2) [23], perchlorates, nitrates, carbonates [70d], and tetrafluoroboranates [70e].

5. Preparation of Organotin Hydrides

Although trimethyltin hydride was prepared by *Kraus* and *Greer* [71] as early as 1922, most organotin hydrides have long been considered as difficult to synthetize and unstable [1,2]. However, they can now be prepared from organotin halides [10,72–76,91] or stannoxanes [75a] by reduction with lithium aluminum hydride. Excellent results are also obtained with dialkylaluminum hydrides [76–78], which are now readily available [13]. Organotin hydrides are prepared in good yield at −20 °C to 0 °C according to the following equations:

$$R_3SnCl + R'_2AlH \rightarrow R_3SnH + R'_2AlCl$$
$$R_2SnCl_2 + 2\,R'_2AlH \rightarrow R_2SnH_2 + 2\,R'_2AlCl$$
$$RSnCl_3 + 3\,R'_2AlH \rightarrow RSnH_3 + 3\,R'_2AlCl.$$

No solvents are necessary. The reaction product can usually be distilled off directly. The residual organoaluminum compounds can be used for preparing further tin alkyls (see Sects. 2 and 3). New organotin hydrides have been prepared by this method, others for the first time in large quantities or in pure form [76,77,91].

If contact with air (and other oxidants), acids, metals, and greasy glassware is carefully avoided, it is possible to store pure monohydrides for a practically unlimited time without decomposition; pure dihydrides may be kept for several weeks and pure trihydrides for at least a few days. Thus it is possible to distill diphenyltin dihydride without decomposition. Preparations which contain traces of the above impurities decompose more or less rapidly with disproportionation, the primary product, stannic hydride, decomposing extensively and spontaneously in most cases [76,77]:

$$4\,R_3SnH \rightarrow 3\,R_4Sn + Sn + 2\,H_2$$
$$2\,R_2SnH_2 \rightarrow R_4Sn + Sn + 2\,H_2$$
$$4\,RSnH_3 \rightarrow R_4Sn + 3\,Sn + 6\,H_2$$

Mechanisms that were previously postulated for the decomposition [73] could not be confirmed. The trihydrides are transformed into intermediate red oils with structures which are now under investigation [79].

The organotin hydrides studied so far are colorless, distillable liquids and are monomeric in solution [2,76]. Their infrared spectra are characterized by very intense, sharp Sn-H absorption peaks [73,74,80]. The physical constants of several important organotin hydrides are summarized in Table 1 [80a].

In addition to the generally applicable preparative methods, there are a few of special importance. Thus,

Table 1. Physical constants of some organotin hydrides

	B. p. [°C/mm Hg]	n_D^{20}	d_4^{20}	$\nu_{Sn\text{-}H}$ [*] [cm^{-1}]
$(C_2H_5)_3SnH$	148–150	1.4709	1.250	1800
	37–38/12	1.4700 [10]	1,258 [10]	
$(C_2H_5)_2SnH_2$	96–98	1.4679	1,27	1822
$(C_2H_5)SnH_3$	22–23	1.4490	—	1869 [81]
				1869
$(nC_4H_9)_3SnH$	65–67/0.6	1.4726	1.104	1820
$(nC_4H_9)_2SnH_2$	70/12	1.4703	1.19	1835
$nC_4H_9SnH_3$	98–100	1.4609	1.14	1855
$(C_6H_5)_3SnH$	131–134/0.004 [+]	1.6322(28 °C)	1.378 [**]	1850
$(C_6H_5)_2SnH_2$	89–93/0.3	1.5951	1,39	1855
$(C_6H_5)SnH_3$	57–64/106	1,4370 [++]	—	1880

[+] The previous value of 80–81 °C/12 [82] could not be confirmed.
[++] The compound contained traces of ether.
[*] Measured in dilute cyclohexane solution.
[**] Supercooled melt.

[69] German Published Patent Application 1 121 050 (Dec. 9th, 1960), inventors *E. Wiberg* and *R. Rieger*.

[70] *G. J. M. van der Kerk, J. G. A. Luijten*, and *M. J. Janssen*, Chimia *16*, 10 (1962); Recueil trav. chim. Pays-Bas *81*, 202 (1962).

[70a] *K. Jones* and *M. F. Lappert*, Proc. chem. Soc. (London) 358 [1162]; *E. W. Abel, D. Brandy*, and *B. R. Lerwill*, Chem. and Ind. (193 (1962); *K. Sisido* and *S. Kozima*, J. org. Chemistry *27*, 4051 33962).

[70b] *J. R. Beattie, G. P. McQuillen*, and *R. Hulme*, Chem. and Ind. 1429 (1962).

[70c] *M. J. Janssen, J. G. A. Luijten*, and *G. J. M. van der Kerk*, Recueil trav. chim. Pays-Bas *82*, 90 (1963).

[70d] *R. Okawara, B. J. Hathaway* and *D. E. Webster*, Proc. chem. Soc. (London) 13 (1963).

[70e] *B. J. Hathaway* and *D. E. Webster*, Proc. chem. Soc. (London) 14 (1963).

[71] *C. A. Kraus* and *W. N. Greer*, J. Amer. chem. Soc. *44*, 2629 (1922).

[72] *A. E. Finholt, A. C. Bond Jr., K. E. Wilzbach*, and *H. I. Schlesinger*, J. Amer. chem. Soc. *69*, 2692 (1947).

[73] *R. Mathis-Noel, M. Lesbre*, and *I. S. de Roch*, C. R. hebd. Séances Acad. Sci. *243*, 257 (1956).

[74] *M. Lesbre* and *I. S. de Roch*, Bull. Soc. chim. France [5] *J*, 754 (1956).

[75] *G. J. M. van der Kerk, J. G. Noltes*, and *J. G. A. Luijten*, J. appl. Chem. *7*, 366 (1957).

[75a] *W. J. Considine* and *J. J. Ventura*, Chem. and Ind. 1683 (1962).

[76] *W. P. Neumann* and *H. Niermann*, Liebigs Ann. Chem. *653*, 164 (1962).

[77] *W. P. Neumann*, Angew. Chem. *73*, 542 (1961).

[78] German Published Patent Application 1 117 577 (Nov. 5th, 1958), German Published Patent Application 1 117 090 (Oct. 3rd, 1958), Kali-Chemie A.-G., inventor *H. Jenkner*.

[79] *W. P. Neumann* et al., unpublished.

[80] *H. Kriegsmann* and *S. Pischtschan*, Z. anorg. allg. Chem. *308*, 212 (1961).

[80a] The values were measured by *W. P. Neumann* et al. unless indicated otherwise.

triphenyltin hydride may be obtained by hydrolysis of $[(C_6H_5)_3Sn]_2Mg$ [51]. Lower alkyl di- and trihydrides are made [81,83] from the sodium derivatives, which themselves may be prepared from stannic hydride.

6. Syntheses with Organotin Hydrides

Organotin hydrides have been used for many kinds of syntheses, among them the preparation of alkyltin derivatives containing functional groups in the organic residues. Two possible modes of reaction are available:

a) organotin hydrides add onto unsaturated systems;

b) the hydride hydrogen is split off with protons as H_2 or transferred to another molecule.

a) Addition to Unsaturated Systems

Organotin hydrides add onto α-olefins and acetylenic compounds [84,85]:

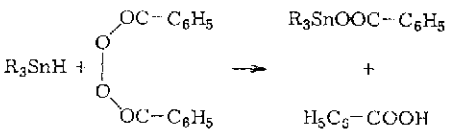
$$R_3SnH + H_2C{=}CH{-}R' \rightarrow R_3Sn{-}CH_2{-}CH_2{-}R'$$
$$R_3SnH + HC{\equiv}C{-}R' \rightarrow R_3Sn{-}CH{=}CH{-}R'$$

The latter reaction has been found to proceed rapidly and exothermally with every alkyne with which it has been attempted. On the other hand, α-olefins react only with highly active aryltin hydrides, whereas the aliphatic organotin hydrides, that are more readily available (see Sect. 5), undergo addition to olefinic bonds only when the latter are activated by conjugation with an unsaturated group. Numerous syntheses with such activated olefins and with vinylmetallic compounds have been carried out [84–87]. Attempts to catalyze this reaction (by analogy with reactions of the silicon compounds) with hexachloroplatinic acid, free radical sources, or radiation have not been successful. It appeared that free radicals were not involved in the mechanism of addition of organotin hydrides to olefins [88,89].

We have found, however, that the addition does in fact proceed by a free radical mechanism, and can be efficiently catalyzed by radical sources which decompose at low temperatures. It is now possible to add not only alkyltin monohydrides but also di- and trihydrides to almost any α-olefin [90–93]. The organotin group is always attached to the terminal carbon atom [84,91,94]:

$$R_3SnH + H_2C{=}CH{-}R' \rightarrow R_3Sn{-}CH_2{-}CH_2{-}R'$$
$$R_2SnH_2 + 2\,H_2C{=}CH{-}R' \rightarrow R_2Sn(CH_2{-}CH_2{-}R')_2$$
$$RSnH_3 + 3\,H_2C{=}CH{-}R' \rightarrow RSn(CH_2{-}CH_2{-}R')_3.$$

The residue R′ may contain various functional groups, including internal carbon-carbon double bonds [90–93]. Table 2 gives a few examples of such additions including some reactions with olefins possessing two conjugated unsaturated groups. These had already been converted in the past without using catalysts, but catalysis made possible a significant lowering of the reaction temperature or a shortening of the required reaction time. The addition reaction with vinyl acetate affords a good example. Without the use of a catalyst, ethylene is evolved during the reaction [82], whereas good yields are now obtained. Azo-bis-isobutyronitrile and the corresponding esters, benzyl hyponitrite, phenylazo-isobutyronitrile, and other free-radical sources have been shown to be useful catalysts. The most favorable reaction temperatures usually lie between 30 and 80 °C. Earlier failures using benzoyl peroxide [88] can now be explained by fast chain termination reactions which compete with the addition of the olefin [90,91,93].



The benzoic acid reacts with additional organotin hydride, with evolution of H_2 and formation of another molecule of trialkyltin benzoate.

These catalysts, and also $ZnCl_2$, promote addition of organotin hydrides to azomethines and carbonyl compounds [90,95,95a]. The reaction with alkynes [90], including acetylene [96], is also strongly accelerated.

$$(C_2H_5)_3SnH + C_6H_5{-}N{=}CH{-}C_6H_5 \rightarrow (C_2H_5)_3Sn{-}N(C_6H_5){-}CH_2{-}C_6H_5$$
$$(C_2H_5)_3SnH + O{=}CHC_6H_5 \rightarrow (C_2H_5)_3Sn{-}O{-}CH_2{-}C_6H_5$$
$$(C_2H_5)_3SnH + HC{\equiv}C{-}CH_2OH \rightarrow (C_2H_5)_3Sn{-}CH{=}CH{-}CH_2OH$$

Some additions are also made possible by the use of ultraviolet light [96a]. A great variety of alkyltin compounds can be prepared in this manner, the more so when reactants are used which are capable of adding the hydride at two or more positions, thus leading to polyadditions yielding organotin macromolecules (see Sect. 8).

[81] *H. J. Emeléus* and *S. F. A. Kettle*, J. chem. Soc. (London) 2444 (1958).

[82] *J. G. Noltes* and *G. J. M. van der Kerk*: Functionally Substituted Organotin Compounds. Tin Res. Inst. Greenford, England, 1958.

[83] *S. F. A. Kettle*, J. chem. Soc. (London) 2936 (1959).

[84] *G. J. M. van der Kerk*, *J. G. Noltes*, and *J. G. A. Luijten*, J. appl. Chem. *7*, 356 (1957).

[85] *G. J. M. van der Kerk* and *J. G. Noltes*, J. appl. Chem. *9*, 106 (1959).

[86] *M. C. Henry* and *J. G. Noltes*, J. Amer. chem. Soc. *82*, 558, 561 (1960).

[87] *J. G. Noltes* and *G. J. M. van der Kerk*, Recueil Trav. chim. Pays-Bas *80*, 623 (1961); *81*, 41 (1962).

[88] *H. Gilman* and *J. Eisch*, J. org. Chemistry *20*, 763 (1955).

[89] *R. Fuchs* and *H. Gilman*, J. org. Chemistry *22*, 1009 (1957).

[90] *W. P. Neumann*, *H. Niermann*, and *R. Sommer*, Angew. Chem. *73*, 768 (1961).

[91] *W. P. Neumann*, *H. Niermann*, and *R. Sommer*, Liebigs Ann. Chem. *659*, 27 (1962).

[92] *H. Niermann*, Ph. D. thesis, Universität Gießen 1961.

[93] *R. Sommer*, diploma thesis, Universität Gießen 1961.

[94] See *G. Natta*, *P. Pino*, *G. Mazzanti*, *P. Longi*, and *F. Bernardini*, J. Amer. chem. Soc. *81*, 2561 (1959), further references are given here.

[95] *W. P. Neumann* and *E. Heymann*, unpublished.

[95a] *W. P. Neumann* and *E. Heymann*, Angew. Chem. internat. Edit. *2*, 100 (1963).

[96] *E. M. Smolin*, Tetrahedron Letters *1961*, 143.

[96a] *R. Calas*, *J. Valade*, and *J. C. Pommier*, C. R. hebd. Séances Acad. Sci. *255*, 1450 (1962).

Table 2. Catalyzed addition of organotin hydrides onto α-olefins [90–93]

Organotin hydride	Olefin	Catalyst	Product	React. temp. [°C]	React. time [hr]	B.p. [°C/mm Hg]	n_D^{20}	Yield [*] [%]
$(C_2H_5)_3SnH$	1-Octene	a	$(C_2H_5)_3Sn-(CH_2)_7-CH_3$	80–90	78	86–87/0.1	1.4713	98
$(C_2H_5)_3SnH$	1-Vinylcyclohex-3-ene	d	$(C_2H_5)_3Sn-(CH_2)_2-$	80–90	50	81.5/0.2	1.5120	53
$(C_2H_5)_3SnH$	Ethyl ω-undecylenoate	d	$(C_2H_5)_3Sn-(CH_2)_{10}-COOC_2H_5$	40–50	50	110/10^{-4}	1.4738	78
$(C_2H_5)_3SnH$	α-Methylstyrene	d	$(C_2H_5)_3Sn-CH_2-CH(CH_3)-C_6H_5$	60–70	21	152–157/13	1.5279	79
$(C_2H_5)_3SnH$	*N*-Vinylcarbazole	d	$(C_2H_5)_3Sn-(CH_2)_2-NC_{12}H_8$	70–80	20	205–210/10^{-3}	1.6140	82
$(C_2H_5)_3SnH$	Vinyl acetate	d	$(C_2H_5)_3Sn-(CH_2)_2-OOCCH_3$	30–40	2	52–56/10^{-4}	1.4773	65
$(C_2H_5)_3SnH$	Methyl acrylate	b	$(C_2H_5)_3Sn-(CH_2)_2-COOCH_3$	40	2.5	117–119/11	1.4793	93
$(C_2H_5)_3SnH$	Methacrylamide	d	$(C_2H_5)_3Sn-CH_2-CH(CH_3)-CONH_2$	40–50	15	136–138/10^{-3}		67
$(C_2H_5)_3SnH$	Acrylonitrile	c	$(C_2H_5)_3Sn-(CH_2)_2-CN$	40–50	1.5	128–130/12	1.4912	79
$(C_2H_5)_3SnH$	Vinyl isobutyl ether	d	$(C_2H_5)_3Sn-(CH_2)_2-OCH_2-CH(CH_3)_2$	50–60	29	122/14	1.4719	87
$(C_2H_5)_3SnH$	Diallyl	d	$(C_2H_5)_3Sn-(CH_2)_4-CH=CH_2$	50–70	18	115–119/13	1.4820	72
$(C_2H_5)_3SnH$	1,7-Octadiene	d	$(C_2H_5)_3Sn-(CH_2)_6-CH=CH_2$	80	25–30	143–146/12	1.4845	65
$(C_4H_9)_3SnH$	Allyl alcohol	d	$(C_4H_9)_3Sn-(CH_2)_3-OH$	50–60	2	173–176/12	1.4887	89
$(C_2H_5)_2SnH_2$	Styrene	d	$(C_2H_5)_2Sn[(CH_2)_2C_6H_5]_2$	60–70	12	142–145/10^{-3}	1.5645	85
$(C_2H_5)_2SnH_2$	Hydroxyethyl allyl ether	d	$(C_2H_5)_2Sn[(CH_2)_3-O-(CH_2)_2-OH]_2$	50–60	11	173–177/10^{-3}	1.5025	55
$C_4H_9SnH_3$	Methyl methacrylate	d	$C_4H_9-Sn[CH_2-CH(CH_3)-COOCH_3]_3$	50	5	150–154/10^{-3}	1.4836	75

[*] Some of the reactions were performed on a very small scale. Better yields should be expected when larger amounts are used.
Catalysts: a) Phenylazotriphenylmethane; b) diethyl azo-bis-isobutyrate; c) benzyl hyponitrite; d) azo-bis-isobutyronitrile.

b) Reactions with Elimination of Hydride Ion

Owing to the polarizability of the tin–hydrogen bond to $Sn^{\oplus}-H^{\ominus}$, organotin hydrides react rapidly and quantitatively with organic and inorganic acids [2,92,96b], *e.g.*,

$$R_3SnH + HOOC-C_6H_5 \rightarrow R_3Sn-OOC-C_6H_5 + H_2$$

The acidity of most phenols, mercapto compounds, and alcohols is not sufficient for such a spontaneous reaction. The reaction starts at once, however, if more acidic complexes, *e.g.*, complexes with $ZnCl_2$, are used [92,93]. Catalytic amounts of the complex-former are sufficient.

Triphenyltin hydride and diphenyltin dihydride can also be used for selective hydrogenations at elevated temperatures: (α,β-unsaturated) ketones give (unsaturated) carbinols [97,98], while sulfones, sulfoxides, and some nitro compounds are reduced to the corresponding SH or NH_2 compounds [98]. The organotin residue is recovered in an easily separable form: monohydrides yield compounds of the type $R_3Sn-SnR_3$, and diphenyltin dihydride yields sparingly soluble diphenyltin. No tin-containing intermediates have yet been observed in these reductions. Aliphatic mono- or dihydrides, too, can be used for selective hydrogenations, especially in the presence of catalysts [98a]. By using the catalysts mentioned above (Sect. 6a), it is often possible to achieve either selective addition of the organotin hydride or selective reduction of the unsaturated compound.

Triphenyltin hydride, like other organotin hydrides, causes replacement of halogen by hydrogen in numerous aliphatic and aromatic halides. Some primary aliphatic amines also seem to have been converted into the respective hydrocarbons by this method [98–100]. However, these results have to be reinvestigated, since it was shown that no ammonia is split out [100a].

7. Unsaturated Alkyltin Compounds

Unsaturated tin alkyls behave differently in many respects from the saturated compounds. Vinyltin compounds are now easily obtainable [101,102]. In addition to investigating preparative methods for numerous vinyl, allyl, methallyl, and other unsaturated tin alkyls, *Seyferth* and co-workers carried out detailed studies of the great mobility of alkenyl residues attached to tin and its application to transmetallation reactions. Thus, alkenyl-lithium compounds are obtained smoothly from phenyl- or n-butyl-lithium [103–105]. Apparently there

[96b] *S. Weber* and *E. I. Becker*, J. org. Chemistry *27*, 1258 (1962); *A. K. Sawyer* and *H. G. Kuivila*, ibid. 610, 837.

[97] *H. G. Kuivila* and *O. F. Beumel Jr.*, J. Amer. chem. Soc. *80*, 3798 (1958); *83*, 1246 (1961); see also *J. Valade*, *M. Pereyre*, and *R. Calas*, C. R. hebd. Séances Acad. Sci. *253*, 1216 (1961); US.-Pat. 2997485 (July 17th, 1958), Research Corp., inventors *H. G. Kuivila* and *O. F. Beumel Jr.*

[98] *G. J. M. van der Kerk*, *J. G. Noltes*, and *J. G. A. Luijten*, J. appl. Chem. *7*, 360 (1957); *J. G. Noltes* and *G. J. M. van der Kerk*, Chem. and Ind. 294 (1959).

[98a] *W. P. Neumann* and *F. Kleiner*, unpublished.

[99] *L. A. Rothmann* and *E. I. Becker*, J. org. Chemistry *25*, 2203 (1960); *D. H. Lorenz* and *E. I. Becker*, ibid. *27*, 3370 (1962).

[100] *E. J. Kupchik* and *R. E. Conolly*, J. org. Chemistry *26*, 4747 (1961); *E. J. Kupchik* and *R. J. Kiesel*, Chem. and Ind. 1654 (1962); *H. G. Kuivila* and *L. W. Menapace*, J. Amer. chem. Soc. *84*, 3584 (1962).

[100a] *G. J. M. van der Kerk*, *J. G. Noltes*, and *J. G. A. Luijten*, Recueil Trav. chim. Pays-Bas *81*, 853 (1962); *A. Stern* and *E. I. Becker*, J. org. Chemistry *27*, 4052 (1962).

[101] French Pat. 1153234 (June 11th, 1956) with additions of May 10th, 1957, Soc. Usines chim. Rhone-Poulenc, inventor *E. Evieux*.

[102] *D. Seyferth*, Org. Syntheses *39*, 10 (1959).

[103] *D. Seyferth* and *M. A. Weiner*, Chem. and Ind. 402 (1959); J. org. Chemistry *24*, 1395 (1959); *26*, 4797 (1961).

[104] *D. Seyferth*, *G. Raab*, and *K. A. Brändle*, J. org. Chemistry *26*, 2934 (1961).

[105] *D. Seyferth* and *M. A. Weiner*, J. Amer. chem. Soc. *84*, 361 (1962).

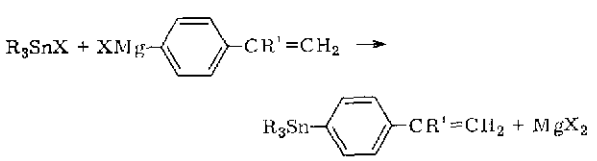
is an equilibrium with a position which depends on the distance of the double bond from the tin atom. Migrations of alkyl groups are also possible between tin tetraalkenyls or -aryls and thallium trichloride: even at room temperature, a yield of 70–90 % R_2TlCl or $RTlCl_2$ or a mixture of the two, is obtained [106]. The configuration of the propenyl residue is retained in transmetallations with propenyltin, propenylmercury, and propenylthallium compounds [107]. *Stone* and *King* [108] studied tetravinyltin, vinyltin halides, and the reaction with iron pentacarbonyl. Progress has also been made in investigations of acetylene- and vinylacetylene-tin compounds [109–111].

8. Polymers Containing Tin

Two routes to organotin macromolecules are conceivable: a) a tin-containing residue is attached to a polymerizable compound which is subsequently polymerized; generally, the tin atom will then not appear in the main chain, or b) a di- or trifunctional tin derivative is used as starting material for a polyaddition or polycondensation reaction leading to macromolecules. The tin atoms then form part of the main chain.

a) Macromolecules with Organotin Substituents

Polymerization of vinyl- and allyltin compounds has so far not been achieved. These compounds even act as polymerization inhibitors [112,113]. It is, however, possible to substitute acrylic, methacrylic, and cinnamic esters with alkyltin groups, and then to proceed with polymerization [113–115]. Styrene and α-methylstyrene with trialkyltin substituents on the benzene ring have also been polymerized. The starting material is usually the *p*-styrylmagnesium halide [116]:



[106] *A. E. Borisov* and *N. V. Novikova*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk 1670 (1959).

[107] *A. N. Nesmeyanov*, *A. E. Borisov*, and *N. V. Novikova*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *259*, 1216 (1959).

[108] *R. B. King* and *F. G. A. Stone*, J. Amer. chem. Soc. *82*, 3833 (1960).

[109] *H. Hartmann*, *H. Niemöller*, *W. Reiss*, and *B. Karbstein*, Naturwissenschaften *46*, 321 (1959); *H. Hartmann*, *E. Dietz*, *K. Komorniczyk*, and *W. Reiss*, Naturwissenschaften *48*, 570 (1961).

[110] *A. A. Petrov*, *S. V. Zavgorodnij*, Zh. obshch. Khim. *30*, 1055 (1960); Dokl. Akad. Nauk SSSR *143*, 855 (1962).

[111] *M. LeQuan* and *P. Cadiot*, C. R. hebd. Séances Acad. Sci. *254*, 133 (1962).

[112] *M. M. Koton*, *T. M. Kiseleva*, *N. P. Zapevalova*, Zh. obshch. Khim. *30*, 186 (1960).

[113] A review is given by *D. Braun*, Angew. Chem. *73*, 197 (1961).

[114] Russ. Pat. 139833 (Febr. 11th, 1960), inventor *D. A. Kočkin*.

[115] *M. F. Shostakovskii*, *V. N. Kotrelev*, *G. I. Kuznetsova*, *S. P. Kalinina*, *L. V. Laine*, and *A. I. Borisova*, Vysokomolekulyarnye Soyedineniya *3*, 1128, 1131 (1961).

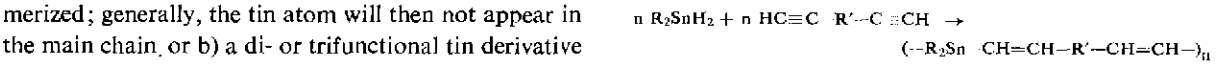
[116] *J. R. Leebrick* and *H. E. Ramsden*, J. org. Chemistry *23*, 935 (1958).

Such syntheses have been performed with R = H, methyl, ethyl, and phenyl [116–119].

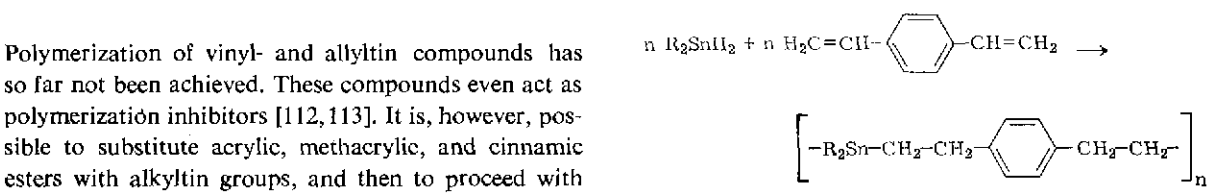
Tin alkyls with epoxy groups can be polymerized [120,121], and polyaddition of epoxides onto organotin halides has been reported [122]. Of curse, one could introduce residues containing tin subsequently into preformed polymers, *e.g.*, *via* the *p*-lithium compound of polystyrene [113]; however, although this type of reaction proceeds readily with the trimethylsilane residue, introduction of organotin groups has so far encountered difficulties, apparently of a steric nature.

b) Macromolecules with Tin in the Main Chain

The addition of organotin hydrides to unsaturated compounds (see Sect. 6a) becomes a polyaddition when di- or trihydrides and polyfunctional unsaturated compounds are used. α,ω-Diynes such as 1,5-hexadiyne, 1,8-nonadiyne, or *p*-diethynylbenzene are easily and exothermally converted into linear macromolecules



average molecular weights of 45000 to 100000 being obtained [123]. The highly reactive compound *p*-divinylbenzene was converted into a vitreous polymer in this manner [123] (R = C_6H_5):



Polyaddition with unactivated α,ω-dienes such as 1,7-octadiene and 1,2,4-trivinylcyclohexane [124] can be achieved with the aid of catalysts (see Sect. 6a) [91,125].

In addition to dialkyltin dihydrides, (*e.g.* diethyltin dihydride), alkyltin trihydrides (*e.g.* isobutyltin trihydride) have been used. Similarly, reactive trienes (such as trivinylcyclohexane) have been employed instead of α,ω-dienes. The ratio of Sn–H groups to terminal double bonds does not necessarily have to be exactly 1:1. On the contrary, excess unsaturated groups can be used subsequently for cross-linking or other reactions [125].

[117] *V. V. Korshak*, *A. M. Polyakova*, and *E. S. Tamboutseva*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk 742 (1959).

[118] *J. G. Noltes*, *H. A. Budding*, and *G. J. M. van der Kerk*, Recueil Trav. chim. Pays-Bas *79*, 408, 1076 (1960).

[119] *A. D. Petrov*, *E. A. Chernychev* and *T. L. Krasnova*, Dokl. Akad. Nauk SSSR *140*, 837 (1961).

[120] German Published Patent Application 1116666 (July 19th, 1957), Metal and Thermit Corp., inventor *G. P. Mack*.

[121] Russ. Pat. 138621, 138622, 138623 (Aug. 29th, 1960), inventors *A. Wende* et al.

[122] German Published Patent Application 1079329 (May 15th, 1956), Farbwerke Hoechst A.-G., inventors *C. Dörfelt*, *E. Reindl* and *K. Härtel*.

[123] *J. G. Noltes* and *G. J. M. van der Kerk*, Recueil Trav. chim. Pays-Bas *80*, 623 (1961); *81*, 41 (1962).

[124] Preparation: *R. K. Rienäcker*, Ph. D. thesis, Universität Bern, 1958, and personal communication.

[125] *W. P. Neumann* and *R. Sommer*, unpublished.

In addition to polymers with main chains consisting of carbon and tin atoms, polystannoxanes, in which tin and oxygen atoms alternate in the principal chain, are also known [125a]. These are the tin analogs of the silicones and are prepared by polycondensation of dialkyltin dialkoxides [126], from dialkyltin dichlorides and organosilicon compounds [127, 128], from dialkyltin diacetates [129] (also in mixtures with tin tetraethoxide [130]), or from alkyltin trichlorides. On hydrolysis, the latter yield alkylstannic acids, which lose water to form high polymers [131] if the water is removed by azeotropic distillation. Long-chain esters with molecular weights of approx. 3000 have also been prepared from dibutyltin oxide (or diacetate) and higher dicarboxylic acids [132].

9. The "Dialkyltin" Problem

Although a diethyltin was described by *Löwig* [133] as early as 1852, the group of dialkyltins is still discussed only with considerable reserve [125a]. Recent work has established the structures of diethyltin [137, 138] and diphenyltin [146, 147].

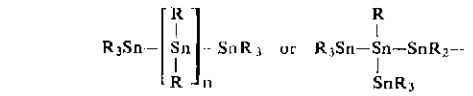
a) Diethyltin

Diethyltin has been variously described as a red, yellow, or colorless oil and as a yellow solid [134, 135a]. It is inconceivable that the various authors were dealing with the same substance [135]. The materials have usually been designated as polymers, but molecular weight determinations have been published only in one case [135a]. At present, the structure of the products can only be conjectured [2, 125a, 136]. The substances have been characterized only by elemental analysis, any unsatisfactory results being ascribed to impurities. However, even agreement with the calculated values does not prove that two ethyl groups are attached to each tin atom. Therefore this problem had to be tackled first.

Degradation with bromine or, preferably, chlorine at −70 °C [137, 138] causes cleavage of Sn–Sn bonds only. Polymeric diethyltin should then give diethyltin dichloride as the only degradation product:

$$[(C_2H_5)_2Sn]_n + n\,Cl_2 \rightarrow n\,(C_2H_5)_2SnCl_2$$

Instead, every diethyltin preparation investigated has always yielded triethyltin chloride in addition, or even ethyltin trichloride as well. These compounds originate only from structures such as



The deeper the color of a particular "diethyltin" preparation, the higher the degree of branching of the tin chain observed on degradation. These substances are therefore not to be regarded as dialkyltins but as chain compounds [139] with chain ends that are saturated by alkyl groups.

By using finely divided tin as catalyst, we were able to split off hydrogen from diethyltin dihydride and obtained a polymeric ethyltin hydride intermediate, which was ultimately (although very slowly) converted into diethyltin [140]:

$$n\,(C_2H_5)_2SnH_2 \xrightarrow[80\text{–}100\,^\circ C]{Sn} H\text{–}[(C_2H_5)_2Sn]_n\text{–}H + (n-1)\,H_2$$

$$\downarrow \longrightarrow [(C_2H_5)_2Sn]_n + H_2$$

The molecular weights observed depended on the conditions under which the hydrogen was evolved and corresponded to an average of n = 6–9. When organic bases, particularly pyridine or aniline, are used as catalysts [137, 138], the evolution of H_2 proceeds even at 20–50 °C and is complete after a few hours. The molecular weights of the waxy, light yellow, highly air-sensitive products are not dependent upon concentration, the average degree of polymerization being usually 6. Degradation with chlorine affects only diethyltin dichloride and therefore has shown unequivocally that the material is polymeric diethyltin. The results of NMR spectral studies [141] and of all other analytical work strongly suggest a cyclic structure; thus, we are evidently dealing with dodecaethyl-hexastannacyclohexane. Slight variations of the reaction gave us a nearly quantitative yield of well crystallized $[(C_2H_5)_2Sn]_9$ [138].

These compounds react with aluminum chloride, boron fluoride, ferric chloride, ethylmagnesium bromide, and other substances to give yellow or red oils with open and sometimes branched tin chains [137, 138] identical with most of the earlier mentioned oily and colored "tin dialkyls" [133, 134, 135a]. Mention might be made in

[125a] Review: *F. G. A. Stone* and *W. A. G. Graham:* Inorganic Polymers. Academic Press, New York 1962, p. 321 et seq.

[126] German Pat. 970731 (May 13rd, 1955), Montecatini, inventors *V. Cappuccio* and *A. Cittadini*.

[127] *R. Okawara* and *E. G. Rochow:* Organotin Polymers. Harvard University, Cambridge, Mass. 1960, p. 24.

[128] *R. Okawara, D. G. White, K. Fujitani*, and *H. Sato*, J. Amer. chem. Soc. *83*, 1342 (1961).

[129] *S. M. Shivuchin, E. D. Dubikova*, and *W. W. Kureev*, Zh. obshch. Khim. *31*, 3106 (1961).

[130] *M. M. Koton* and *T. M. Kiseleva*, Dokl. Akad. Nauk SSSR *130*, 86 (1960).

[131] German Published Patent Application 1087772 (May 25th, 1957), Farbwerke Hoechst A.-G., inventor *C. Dörfelt*.

[132] *T. M. Andrews, F. A. Bower, B. R. La Liberte*, and *J. C. Montermoso*, J. Amer. chem. Soc. *80*, 4102 (1958).

[133] *C. Löwig*, Liebigs Ann. Chem. *84*, 308 (1852).

[134] *A. Cahours*, Liebigs Ann. Chem. *114*, 227 (1860); *E. Frankland*, ibid. *85*, 320 (1853); *P. Pfeiffer*, Ber. dtsch. chem. Ges. *44*, 1269 (1911); *T. Harada*, J. sci. Res. Inst. (Tokyo) *43*, 31 (1948); *E. Krause* and *K. Weinberg*, unpublished, cited by [25]; *J. R. Zietz, S. M. Blitzer, H. E. Redman*, and *G. C. Robinson*, J. org. Chemistry *22*, 60 (1957).

[135] *G. E. Coates:* Organometallic Compounds. 2nd Edit., Methuen, London 1961, p. 200.

[135a] *N. N. Zemlyanskii, E. M. Panov*, and *K. A. Kochechkov*, Dokl. Akad. Nauk SSSR *146*, 1335 (1962).

[136] *R. W. Leeper, L. Summers*, and *H. Gilman*, Chem. Reviews, *54*, 101 (1954).

[137] *W. P. Neumann*, Lecture in Vienna (Austria), Sept. 12th, 1961; Angew. Chem. *74*, 122 (1962).

[138] *W. P. Neumann* and *J. Pedain*, unpublished; *J. Pedain*, diploma thesis, Universität Gießen 1962.

[139] *C. A. Kraus*, and *A. M. Neal*, J. Amer. chem. Soc. *51*, 2403 (1929).

[140] *W. P. Neumann*, cited by [77]; *H. Niermann*, Ph. D. thesis, Universität Gießen 1961.

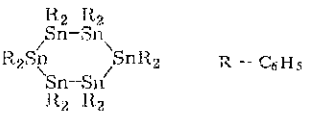
[141] Measured by *E. G. Hoffmann*, Max-Planck-Institut für Kohlenforschung, Mülheim/Ruhr (Germany).

this connection of recent observations of complicated rearrangements of hexamethylditin [142] and hexaethylditin under the influence of the same and similar catalysts [143].

b) Diphenyltin

Here, too, the compounds which have been described range from colorless to intensely red, from monomers to polymers, and from highly air sensitive to stable materials with very different solubilities [2]. A survey is given in [144]. Attempts to clarify the structure of the products were seldom made, characterization being mostly limited to molecular weight determinations, elemental analyses, or even only to determinations of the tin content. Although earlier directions were carefully followed, the values given often could not be reproduced [144,145]. Different products can therefore result from apparently identical procedures. We were able to clarify this situation to a large extent [146,147] by degrading the products with iodine in benzene. Analysis of the fragments (methods: [154,155]) often indicated the presence of appreciable quantities of triphenyltin iodide (and sometimes also of phenyltin triiodide) in addition to the diphenyltin diiodide expected. In particular, the compounds derived from $SnCl_2$ and phenyl-magnesium bromide [148] or phenyl lithium [149] correspond approximately to diphenyltin only in their elemental composition but actually consist of more or less branched phenyl-substituted tin chains. Other, practically insoluble preparations [150] usually yielded a certain amount of diphenyltin oxide. These results explain the large variations between the diverse substances earlier described as "diphenyltin".

Dehydrogenation of diphenyltin dihydride is catalyzed by many aliphatic and aromatic amines [144,146,147], and is a useful method for preparing diphenyltin. The products obtained in this manner consist of $(C_6H_5)_2Sn$ units only, but they vary in the degree and uniformity of polymerization; however, these properties are independent of the age of the preparation. With pyridine as catalyst, mainly the hexamer is obtained. With dimethylformamide one obtains either the hexamer or a good yield of the pentamer, depending on the conditions. Both products are colorless and crystallize well. The pentamer has the structure of decaphenyl-pentastannacyclopentane, and the hexamer that of dodecaphenyl-hexastannacyclohexane [146,147]:



Kuivila and co-workers [144] have also described a diphenyltin which they obtained from diphenyltin dihydride and dimethylformamide. Molecular weight determinations and structural analyses were not published. "Modification B of diphenyltin" [144] has an Sn–H absorption peak in its infrared spectrum and evolves hydrogen when treated with pyridine, being converted to the cyclic hexamer described above. "Modification B" obviously is not diphenyltin, but has the structure $H-[(C_6H_5)_2Sn]_n-H$, where $n \approx 6$ [146].

The demonstration of the ring structures of diethyltin and diphenyltin has thrown some light on this hitherto quite obscure field of organotin chemistry. Further studies are now in progress [138,139]. In this connection, it is noteworthy that ring structures have also been proved for some dialkylsilicon compounds [151,152].

10. Remarks on the Analysis of Organotin Compounds

The results of elemental analyses and sometimes only values for the tin content have usually been used to identify or determine the purity of alkyltin compounds. It is, however, quite difficult to obtain reliable tin values by routine analysis [153]. Several suggestions for improvements have been offered [2,153]. The difficulties attending the correct determination of CH values of organotin compounds should also be kept in mind [2]. The first successful attempts to determine, separately or together, specific organotin groups such as phenyltin, diphenyltin, and triphenyltin residues [154,155] merit attention.

Mixtures of lower tetraalkyltin compounds [156] and alkyltin chlorides [39,157] can be separated very efficiently by gas

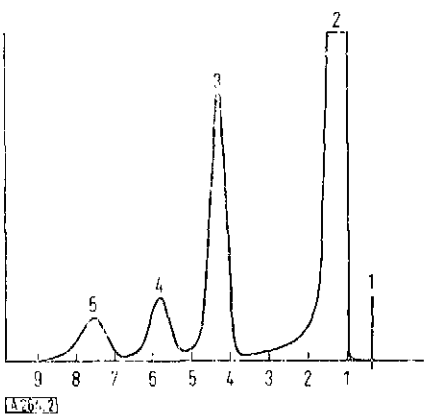


Fig. 2. Resolution of ethyltin chlorides by gas chromatography at 140 °C on a 2 m column filled with silicone oil/Sterchamol [39].
1: Start — 2: Benzene — 3: $C_2H_5SnCl_3$ — 4: $(C_2H_5)_3SnCl$ — 5: $(C_2H_5)_2SnCl_2$
Abscissa: Time [min]

[142] *A. B. Burg* and *J. R. Spielmann*, J. Amer. chem. Soc. *83*, 2667 (1961).

[143] *G. A. Rasuvaev* et al., Dokl. Akad. Nauk SSSR *132*, 364 (1960); Zh. obshch. Khim. *31*, 1401, 1712, 3762 (1961); Tetrahedron *18*, 667 (1962).

[144] *H. G. Kuivila*, *A. K. Sawyer*, and *A. G. Armour*, J. org. Chemistry *26*, 1426 (1961).

[145] *K. A. Jensen*, and *N. Clauson-Kaas*, Z. anorg. allg. Chem. *250*, 277 (1943).

[146] *W. P. Neumann* and *K. König*, Angew. Chem. *74*, 215 (1962).

[147] *W. P. Neumann*, and *K. König*, unpublished; *K. König*, diploma thesis, Universität Gießen 1962.

[148] *E. Krause* and *R. Becker*, Ber. dtsch. chem. Ges. *53*, 173 (1920).

[149] *G. Wittig*, *F. J. Meyer*, and *G. Lange*, Liebigs Ann. Chem. *571*, 169 (1951).

[150] *R. F. Chambers* and *P. C. Scherer*, J. Amer. chem. Soc. *48*, 1054 (1926).

[151] *C. A. Burkhard*, J. Amer. chem. Soc. *71*, 963 (1949).

[152] *H. J. S. Winkler*, *A. W. Jarvie*, *D. J. Peterson*, and *H. Gilman*, J. Amer. chem. Soc. *83*, 4089 (1961), further references are given here.

[153] *M. Farnsworth* and *J. Pekola*, Analytic. Chem. *31*, 410 (1959).

[154] *R. Bock*, *S. Gorbach*, and *H. Oeser*, Angew. Chem. *70*, 272 (1958).

[155] *K. Bürger*, Z. Lebensmittel-Unters. u. -Forsch. *114*, 1 (1961).

[156] *G. Schomburg*, Mülheim/Ruhr (Germany), personal communication.

[157] *W. P. Neumann* et al., unpublished.

chromatography on silicone oil or silicone grease columns (Fig. 2). Columns filled with diisodecyl phthalate are also suitable for many separations [158]. Very little additional data [159] are available at the present time. When vapor-phase chromatography is used, attention must be paid to the possibility that thermally induced modifications or changes in the substances can be catalyzed by the column filling, *e.g.*, in such compounds as the phenyltin halides [157]. Paper chromatography is well suited for separation of these [160] and other alkyltin compounds [161] as is thin-layer chromatography [162]. Infrared spectroscopy is particularly valuable for the investigation of special problems [163], especially for estimations of organotin hydrides [76,91]. The Sn-H absorption peaks in the range from 1800 to 1880 cm^{-1} (see Table 1) are always sharp and of high intensity and are seldom obscured by other absorptions, even in complex mixtures. Samples of low hydride content can be measured directly if air is excluded; those with high hydride content are diluted with cyclohexane to avoid possible decomposition of the organotin hydride at the metallic parts of the measuring cell.

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[158] *H. D. Kaesz, Z. R. Phillips,* and *F. G. A. Stone,* Chem. and Ind. *45*, 1409 (1959).

[159] *J. Franc* and *M. Wurst,* Collect. czechoslov. chem. Commun. *25*, 701 (1960); *J. Franc, M. Wurst,* and *V. Moudry, ibid. 26*, 1313 (1961).

[160] *W. P. Neumann* and *H. Weller,* unpublished.

[161] *R. Barbieri, U. Belluco,* and *G. Tagliavini,* Ann. Chimica *48*, 940 (1958); *O. A. Reutov, O. A. Ptitsyna,* and *M. F. Turtschinskii,* Dokl. Akad. Nauk SSSR *139*, 146 (1961); *J. Gasparič* and *A. Cee,* J. Chromatogr. *8*, 393 (1962).

[162] *K. Bürger,* Z. anal. Chem. *192*, 280 (1963).

[163] *E. Friebe* and *H. Kelker,* Z. anal. Chem. *192*, 267 (1963).

Chemistry and Biochemistry of Insect Hormones

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Dedicated to Prof. Dr. A. Butenandt on the occasion of his 60th birthday

Insect hormones attracted the interest of endocrinologists only comparatively recently. This is partly due to the fact that an equivalent of sex hormones – the classical hormones of vertebrate physiology – is unknown in insects. Castration has no marked effect on the secondary sexual characters. Insect hormones act primarily on developmental processes; the metamorphosis hormone, ecdysone, is the best studied. Recent investigations have shown that ecdysone has the empirical formula $C_{27}H_{44}O_6$ and belongs to the steroids. The mechanism of its action is seen in its influence on the chromosomes. – Other hormone-like substances, the pheromones, are outstanding for their high activity; a few molecules are sufficient to trigger the characteristic behavioural response.

1. Hormonal Control of Insect Development

Insect development takes place through several instars, and often also through a pupal instar (in the case of the so-called holometabolic insects) [1,2]. The change from each instar to the next involves moulting, during which the old chitinous exoskeleton is thrown off and a new one formed.

Moulting is controlled by several hormones. It is initiated by a hormone produced in the neurosecretory cells of the brain, which acts on a subordinate gland, the prothorax. This gland is stimulated by the "prothoracotropic hormone" to produce its own hormone, *viz.* the actual moulting hormone, ecdysone.

In the larva, ecdysone induces moulting to the next instar. In addition, a hormone from the corpora allata is essential for larval moulting. These relationships are shown diagrammatically in Fig. 1.

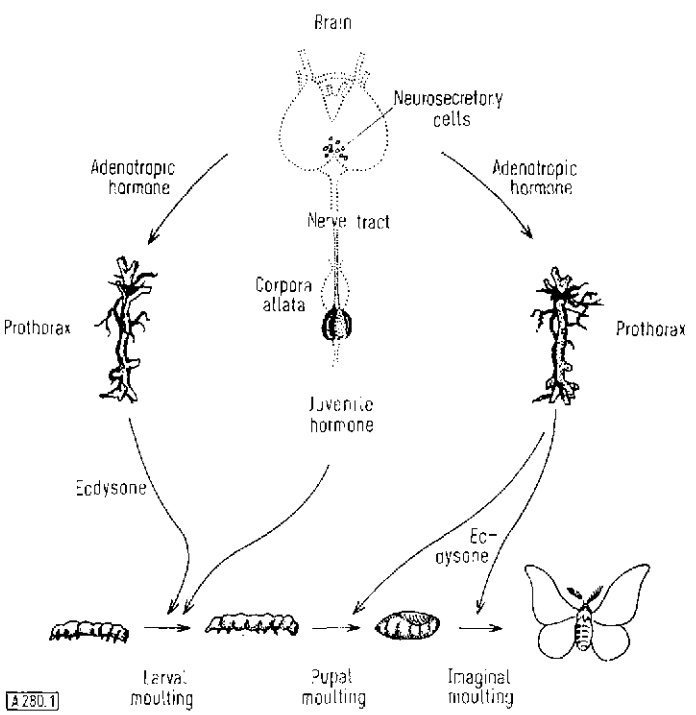


Fig. 1. Action of insect hormones. At the top of the figure, the glands are illustrated which secrete hormones producing the moults shown lower down [2a].

[1] *H. Weber:* Grundriß der Insektenkunde. 3rd Edit., Gustav Fischer, Stuttgart 1953.

[2] *O. Pflugfelder:* Entwicklungsphysiologie der Insekten. 2nd, Edit., Akademische Verlagsgesellschaft, Leipzig 1959.

[2a] From *P. Karlson:* Kurzes Lehrbuch der Biochemie. 3rd Edit., G. Thieme, Stuttgart 1962, p. 309.

In insects, *i.e.* at quite an early stage of phylogenetic development, a system of endocrine glands is recognizable that is quite comparable to that of vertebrates. It is moreover noticeable that for larval moulting not only the moulting hormone but also a special juvenile hormone determining the immature character of the next instar is necessary. However, only the moulting hormone is active in the changes from larva to pupa and from pupa to butterfly; the juvenile hormone is not required.

This complicated state of affairs has confused the nomenclature of insect hormones, especially that of the prothoracic gland hormone. This has been variously known as the 'moulting hormone', the 'metamorphosis hormone', as well as the 'growth and differentiation hormone'. We have named the substance ecdysone, and will use this term in the following. The hormone of the corpora allata has been named juvenile hormone or 'neotenin'; the prothoracotropic hormone is mostly known simply as the brain hormone from its place of origin.

This is not the place to go into the numerous biological experiments which led to this conception and established the scheme given above [3,4]. A few examples should illustrate the methods used and the effects obtained. After surgical removal of the corpora allata, the next moult of a young larva is a pupal ecdysis or, in the case of hemimetabolic insects, moulting to give an adult or adultoid animal. Conversely, after implantation of the glands in mature larvae, the next ecdysis is to a supernumerary larval instar. Similarly, a second pupal instar can be produced in pupae. Ecdysis can be induced by implantation of prothoracic glands; for this experiment larvae can be used which have been ligatured to give an anterior and a posterior portion. The ligatured posterior section, which survives for a considerable time, is a very satisfactory test material. For a long time we have been using posterior sections of blow fly maggots for assaying ecdysone (the *Calliphora* test). Hind portions of hibernating pupae of the giant silkworm moth (*H. cecropia*) show development after injection of ecdysone or gland implantation.

2. The Brain Hormone

The role of the cerebral ganglia as endocrine glands was recognized relatively early: in 1922, *Kopeč* reported on relevant biological experiments [5]. Nevertheless, it was a considerable time before the first active extracts could be prepared.

Current literature on the chemical characteristics of this hormone is contradictory. *Kobayashi* found a definite activity in ether extracts of cerebral ganglia from *Bombyx* [6]. Following this, *Kobayashi* and his co-workers recently reported the isolation of a crystalline substance, which they claim to be active and which they have identified as cholesterol [7,8]. This will however have to await further confirmation. Cholesterol had already been isolated from silkmoths [9] and, according to our own experiments, is present in *Bombyx* pupae in relatively large quantities. This high concentration is not what one would expect if cholesterol is in fact a hormone in the usual sense of the word. If *Kobayashi* has not been the victim of some experimental slip, that is, if the cholesterol isolated by him does not contain a small amount of a highly active hormone as an impurity, the physiological action of cholesterol may perhaps be explained by its conversion into an active substance (*e.g.* ecdysone) [10].

Cholesterol and other steroids occur regularly in the diet of insects, and they are essential nutritional ingredients. This also argues against the hormonal nature of cholesterol. Insects are in fact unable to build up cholesterol or steroids; the biosynthesis is interrupted at the stage of squalene. Regulating hormones must, however, be formed by the organism itself.

Independently of *Kobayashi*, *Schneiderman* [11] found brain hormone activity in lipid extracts from insect tissues. These show also juvenile hormone activity (see below). No attempt at concentrating these extracts has been made.

In contrast to both *Kobayashi* and *Schneiderman*, *Ishikawa* [12] found activity not in the lipid soluble but in the water soluble portion of the extract. He has also reported preliminary stages of concentration, but has not yet obtained a pure preparation. According to data given by *Gersch* [13], the water soluble neurohormone D_1 isolated by him possesses the activity of brain hormone. His assay methods certainly diverge considerably from those of the Japanese workers.

Gersch et al. have crystallized a substance with the action of neurohormone D_1 [14]; but there is only insufficient information at present regarding the chemical nature and uniformity of this material. It will be necessary to wait until larger amounts of the material allow thorough investigation.

The biological action of brain hormone is the stimulation of the prothoracic glands. Whether any further definite effects will be found cannot be decided at this stage. Although there are some such indications from biological experiments, they need confirmation by experiments with active extracts.

3. The Chemistry of Ecdysone

In most insects the prothoracic glands are extensively branched cords of relatively loosely joined cells. They were recognized as hormone secreting glands only comparatively recently. Their removal is possible only in very few species. Hence their action can mostly only be studied by means of transplantation experiments.

Extraction and concentration of this hormone was first attempted by *Becker* and *Plagge* [15]. Working on a discovery by *Fraenkel*, they developed a bioassay which we later improved and made quantitative [16]. This "*Calliphora* test" is shown diagrammatically in Fig. 2.

[3] *P. Karlson*, Vitamins and Hormones *14*, 227 (1956).

[4] *V. A. Novak:* Insektenhormone. Verlag der Akademie der Wissenschaften, Prague 1959.

[5] *S. Kopeč*, Biol. Bull. *42*, 323 (1922).

[6] *M. Kobayashi* and *I. Kirimura*, Nature (London) *181*, 1217 (1958).

[7] *I. Kirimura*, *M. Saito*, and *M. Kobayashi*, Nature (London) *195*, 515 (1962).

[8] *I. Kirimura*, *M. Saito*, and *M. Kobayashi*, Nature (London) *195*, 729 (1962).

[9] *W. Bergman*, J. biol. Chemistry *107*, 527 (1934).

[10] *L. J. Gilbert*, personal communication.

[11] *L. J. Gilbert* and *H. S. Schneiderman*, Nature (London) *184*, 171 (1959).

[12] *U. Ishikawa* and *H. Ishizaka*, Nature (London) *191*, 933 (1961).

[13] *M. Gersch*, Gen. compar. Endocrinol. Suppl. *1*, 322 (1962).

[14] *M. Gersch*, *F. Fischer*, *H. Unger*, and *H. Koch*, Z. Naturforsch. *17b*, 319 (1962).

[15] *E. Becker* and *E. Plagge*, Biol. Zbl. *59*, 326 (1939).

[16] For the history of the development of this work, see *P. Karlson*, Bollet. Zool. Agrar. Bachicolt. *22*, 65 (1957).

Using this bioassay method, we isolated in 1954 the prothoracic gland hormone in pure, crystalline form [17]. Extraction of large quantities of insect material was

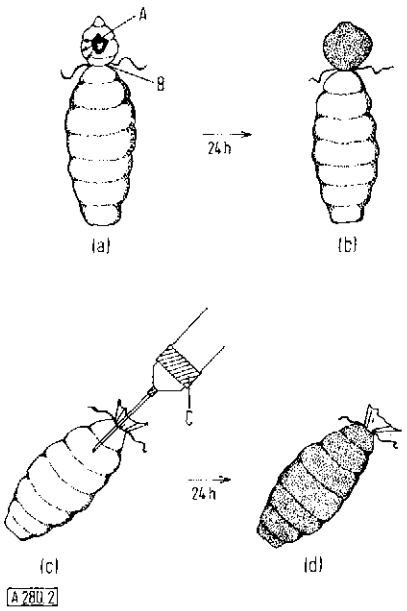


Fig. 2. Bioassay for ecdysone on the blowfly *Calliphora erythrocephala* ('*Calliphora* test'). The larvae are ligatured (a). By this means, the hormone from the anterior portion is unable to diffuse into the posterior portion, and only the anterior part forms a puparium (b). By injection of hormone (c), the hind part can be induced to form a puparium, which is noticeable as a darkening and hardening of the cuticle (d).

A = endocrine gland
B = ligature
C = syringe with hormone solution.

necessary in order to obtain the pure substance. Altogether, approx. 20×10^6-fold concentration was needed; we obtained 25 mg of crystalline hormone from 500 kg of silkworm pupae.

The insects were first extracted with methanol, and the methanol soluble material partitioned between water and butanol. The butanol solution is washed with acid and soda solution and evaporated, giving a concentrate, which can be purified further by various partition procedures as well as by chromatography on alumina. A full account of the method for working up the extracts is given elsewhere [18].

Elucidation of the constitution of ecdysone was a difficult and lengthy task, as only very small amounts of the hormone were available. We intended therefore to tackle the problem with the aid of structural X-ray analysis.

With the state of the X-ray method at that time, a clear-cut structural determination could be made only by using the heavy atom method. A heavy atom must be introduced into the molecule to be examined. This atom is easy to recognize in the reflections and to some extent serves as a starting point for further calculations (especially of the phase angles) [19]. Unfortunately, this line of approach proved impossible, as we did not succeed in obtaining an ecdysone derivative which would crystallize well. This is certainly mainly attributable to the fact that we only had a small amount of material available for preparing the derivatives.

Together with *W. Hoppe* [*], we therefore carried out investigations on ecdysone itself. Firstly, measurement of the unit cell (and density measurements) allowed determination of its molecular weight. It proved to be 464, a value one-and-a-half times the molecular weight of 310, which we had previously assumed.

This new molecular weight, which was later confirmed by mass spectroscopic examination, necessitated revision of its molecular formula. Instead of $C_{18}H_{30}O_4$, a value 1.5 times this, *i.e.* $C_{27}H_{44}O_6$, was taken as the correct formula. Considering that a keto group and a double bond in conjugation with it are present in the molecule, the composition of the fundamental saturated substance can be taken as $C_{27}H_{48}$. This implied that a steroid structure was the basis of the ecdysone molecule, as cholestane has this formula; this suspicion was supported by further X-ray measurements. Using the new "diffuse scattering" method[20],we obtained information on the shape of the molecule, from which a flat, relatively large ring system like that of sterane or perhydroanthracene could be deduced [21].

In the autumn of 1960, by working up a new extract, we obtained somewhat larger amounts of ecdysone (totaling over 200 mg) for the first time. With this it was possible to tackle the problem of the molecular structure by chemical means [21a]. For any newly isolated natural material dehydrogenation to give cyclopentanophenanthrene derivates is regarded as proof of their steroid character. Unfortunately, such dehydrogenations proceed unpredictably and give only very low yields; usually 1–5 g of material are employed to isolate weighable quantities of hydrocarbons [22]. Although we could use only 30 mg of ecdysone, we tried the experiment and finally succeeded in obtaining a fraction of aromatic hydrocarbons. These were separated by thin-layer chromatography. Besides substances which according to their ultraviolet spectra must be naphthalene derivatives, it was possible to isolate a fraction with a phenanthrene spectrum. By paper chromatographic comparison with known preparations, this fraction was shown to contain a methylcyclopentenophenanthrene and 3,3-dimethylcyclopentanophenanthrene [18]. Thus, the steroid nature of ecdysone was further confirmed by classical chemical means.

Ecdysone contains a keto group in conjugation with a double bond, as well as five hydroxyl groups. From its ultraviolet, infrared, and proton resonance spectra, it can be concluded that the keto group is probably at position 12, and the double bond lies between C-9 and C-11. One hydroxyl group is probably on the side chain

[17] *A. Butenandt* and *P. Karlson*, Z. Naturforsch. *9b*, 389 (1954).

[18] *P. Karlson, H. Hoffmeister, W. Hoppe*, and *F. Huber*, Liebigs Ann. Chem., *662*, 1 (1963).

[19] *W. Hoppe*, Angew. Chem. *69*, 659 (1957); *G. Habermehl*, *ibid. 75*, 78 (1963).

[*] Present address: Abteilung für Röntgenstrukturforschung, Max-Planck-Institut für Eiweiß- und Lederforschung, München (Germany).

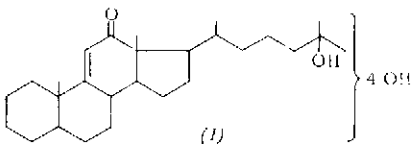
[20] *W. Hoppe*, Z. Kristallogr., Kristallgeometr., Kristallphysik, Kristallchemie *107*, 406 (1956); see also *W. Hoppe:* Fortschritte der Strukturforschung. Vieweg-Verlag, Braunschweig, Vol. 1, in the press.

[21] *F. Huber*, Ph. D. thesis., Technische Hochschule München, 1961.

[21a] Investigations in co-operation with *H. Hoffmeister*.

[22] *M. S. Bharnda, G. Hesse, H. Jäger, E. Weiss*, and *T. Reichstein*, Helv. chim. Acta *45*, 93 (1961); *M. S. Bharda, E. Weiss*, and *T. Reichstein*, ibid. *45*, 103 (1961).

at C-25. Hence the formula of ecdysone, as far as is known at present, is given by structure *(1)*:



(1)

We cannot as yet give any indication of the position of the other hydroxyl groups; and even the partial structure *(1)* requires further confirmation. However, we hope to be able to establish the structure conclusively by a partial synthesis within the foreseeable future.

It seems a strange turn of fate that the insect hormone isolated by *Butenandt* and *Karlson* [17] should be a steroid. *Butenandt* was a student under *Windaus*; however, in Windaus' laboratory he did not work on sterins, but first on rotenone, and later on sex hormones, the chemical nature of which was then completely unknown. The determination of the constitution of the sex hormones led him finally to the field of steroid chemistry. During his stay in Berlin-Dahlem, *Butenandt* then deliberately tackled other problems (biochemical genetics, insect hormones). Now the work on ecdysone, begun in 1943, again opens into the steroid field.

4. The Biogenesis of Ecdysone

Nothing is as yet known of the biogenesis of ecdysone. It is very probably formed from cholesterol, since insects are incapable of a total synthesis of the steroid nucleus [23]. Experiments to establish the conversion of cholesterol into ecdysone are in progress at present [23a].

In the above, we used the fact that sterols are essential dietary factors for insects as an argument against identifying cholesterol with the brain hormone. Naturally this argument does not hold for a derivative of cholesterol; after all, the vertebrate hormones adrenalin and thyroxin are metabolites of the aromatic amino acids tyrosine and phenylalanine, which must be supplied to the organism (phenylalanine is an essential amino acid, tyrosine can be formed from it). It must be assumed that a small part of the ingested cholesterol is converted into ecdysone, while the majority fulfills the same cellular functions as in the vertebrates (*inter alia* as membrane constituent). *Clayton* and *Bloch* [24] already expressed similar ideas when they established that, in the beetle *Dermestes vulpinus*, up to 95% replacement of cholesterol by sitosterol is possible, but that a certain minimal amount of cholesterol is essential and cannot be replaced by sitosterol or similar steroids.

The brain hormone has also been regarded as a biological precursor for ecdysone; several experiments admit of such an interpretation. It may be in this sense that the biological action of injected cholesterol, reported by *Kobayashi*, is to be understood as that of the brain hormone; however, such a substance would certainly not be termed a hormone [*].

Incidentally, many insect species are able to metabolize sitosterol and stigmasterol to cholesterol. These facts have been inferred from dietary balance experiments on *Dermestis maculatus* [23]. Chemically, elimination of single methyl or ethyl groups appears far less understandable than the introduction of hydroxyl groups into the steroid molecule. Numerous examples of this reaction are known already, not only in the biosynthesis of vertebrate hormones – especially in the adrenal cortex – but also in microbiological conversions of steroids, which are even used technically to a considerable extent.

5. The Influence of Ecdysone on Chromosomes

Investigations of the mode of action of ecdysone [25] have given interesting results, which probably have validity beyond the special cases in question. It was in fact shown that ecdysone has a direct influence on genetic material, activating certain gene loci. A general hypothesis of the mechanism of hormone action has been deduced from this finding [26]. The fact that certain insects possess giant chromosomes made the discovery of this relation possible. Detailed examination of the crossbands of giant chromosomes has shown that the functional condition of each individual crossband can be recognized microscopically. Active crossbands appear to be swollen and are termed "puffs" [27]. By means of autoradiography, it can be established that ribonucleic acid is synthetized in the puffed zones.

We have found that ecdysone induces the phenomenon of puffing at a definite gene locus [28]. The effect appears very quickly; changes at the gene locus can be detected microscopically in salivary gland preparations 15–30 minutes after injection. The reaction is also extremely sensitive [29], only small amounts of ecdysone (0.001 *Calliphora* unit = 10^{-5} µg or less) are required. Both these facts indicate that it is a direct action by ecdysone rather than a secondary effect attendant on metamorphosis.

What is the significance of this effect? Biologically speaking, it demonstrates the connecting link between functional genetics and developmental physiology. The genetic determination of most of the characters of organisms is well known. In insects, the characteristics of form and color of larvae and adults are examples, and so are many other characteristics, including in many cases the

[*] The action of glucagon on blood sugar may possibly be taken as an analogy to this. Glucagon mobilizes the sugar reserves, the sugar entering the blood stream increases, and the sugar level rises. The same effect – increase of the blood sugar concentration – can be obtained by injecting glucose. Nevertheless, glucose is not a hormone; the injection has only short-circuited the hormonal processes.

[23] *Z. H. Levinson:* Proceedings XIth International Congress Entomology, Vienna 1960. Istituto Entomologia Universitati Pavia, 1960, Vol. III, p. 145; J. Insect Physiol. *8*, 191 (1962).

[23a] See *P. Karlson* and *H. Hoffmeister*, Hoppe-Seylers Z. physiol. Chem. *331*, 298 (1963).

[24] *R. B. Clayton*, J. biol. Chemistry *235*, 3421 (1960); *A. J. Clark* and *K. Bloch*, J. biol. Chemistry *234*, 2583 (1959).

[25] *P. Karlson:* 8. Symposium der Gesellschaft für Endokrinologie. Springer, Berlin-Göttingen-Heidelberg 1962, p. 90.

[26] *P. Karlson*, Dtsch. med. Wschr. *86*, 668 (1961).

[27] *W. Beermann:* 13. Colloquium der deutschen Gesellschaft für physiologische Chemie. Springer, Berlin-Göttingen-Heidelberg 1963, p. 64.

[28] *U. Clever* and *P. Karlson*, Exp. Cell Res. *20*, 625 (1960).

[29] *U. Clever:* Wissenschaftliche Konferenz der Gesellschaft deutscher Naturforscher und Ärzte. Springer, Berlin-Göttingen-Heidelberg 1963, p. 30.

number of moults. The information on these characteristics is contained in the chromosomes; it is only needed at a definite phase in development. It seems an extremely sensible arrangement that a hormone which produces a definite step in development simultaneously summons the genetic information which is needed at the time.

Biochemically, the action of the hormones on the nucleus can also be well understood. We now know that deoxyribonucleic acids (DNA) – the genetic material – fulfill an important role in protein biosynthesis. They carry the information about the sequence of amino acids in the proteins, as has been verified by many examples [30]. A special ribonucleic acid (RNA) is formed in the DNA chain. This is called the messenger-RNA; it combines with the ribosomes and there directs protein synthesis (Fig. 3). It is now known that many

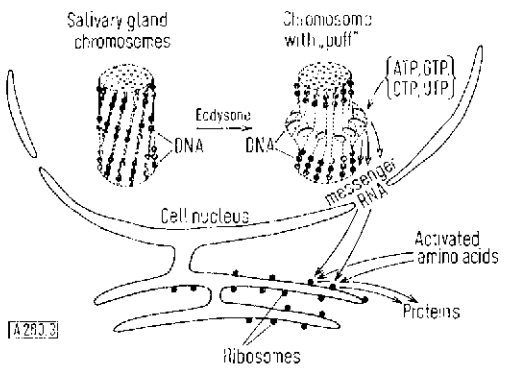


Fig. 3. Diagram showing the action of the hormone. Ecdysone stimulates the synthesis of ribonucleic acid (RNA) in some crossbands of the chromosomes. These crossbands have a swollen appearance ('puffs'). It is assumed that the RNA synthetized acts as messenger-RNA which diffuses out of the nucleus into the cytoplasm and controls protein synthesis on the ribosomes (after [30]).

DNA = deoxyribonucleic acid
ATP = adenosine triphosphate
GTP = guanosine triphosphate
CTP = cytidine triphosphate
UTP = uridine triphosphate

hormones stimulate the synthesis of certain proteins (including enzyme proteins). It is possible to think of several ways in which a hormone could intervene in the mechanism of protein synthesis; if, however, it is to stimulate the synthesis of a definite protein, then it must become active at one of the sites to which the requisite information has been passed on. The simplest assumption is that the hormone controls the synthesis of specific RNA, and that is precisely what we have observed during "puff" formation.

6. Ecdysone and the Tyrosine Metabolism of Insects

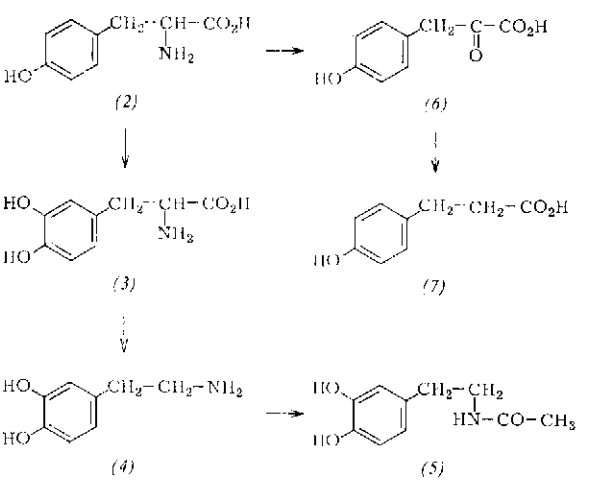
Ecdysone is also one of the hormones which stimulate the activity of certain enzymes. We can demonstrate this with our experimental animal, the blowfly *Calliphora erythrocephala*.

[30] *P. Karlson*, Münchener med. Wschr. *104*, 1697 (1962); Perspect. Biol. Med. 6, 203 (1963).

The *Calliphora* test is based on the fact that the hormone produces puparium formation in the isolated posterior region of the fly maggot. The "puparium" is the hardened, dark brown pigmented larval cuticle, which affords the animal protection during pupation. This envelope arises from the last larval cuticle by a chemical process, which corresponds broadly to quinone tanning in leather production. *o*-Quinones arise by the action of a phenol oxidase and are incorporated into the cuticular proteins. The whole process is called sclerotization.

This process of sclerotization appeared to be a relatively simple and therefore biochemically comprehensible example of a hormonally conditioned morphogenetic reaction. We therefore examined its basic chemical processes. By using ^{14}C labelled compounds, we were able to show that metabolites of tyrosine are deposited in the cuticle. Both diffusely labelled tyrosine and dihydroxyphenylalanine (dopa) proved to be precursors of the sclerotizing quinones, whereas hydroquinone was not incorporated [31].

N-Acetyldopamine can be regarded as the actual sclerotizing substance; experimental data for this belief have been given in detail elsewhere [32]. The metabolic path leading to *N*-acetyldopamine was worked out in cooperation with *Sekeris* [33].



Tyrosine *(2)* is first hydroxylated to dopa. A special enzyme system is responsible for this, probably requiring reduced triphosphopyridine nucleotide. In any case, it does not involve tyrosinase, which plays the decisive role in melanin formation. Dopa *(3)* is then decarboxylated; the dopa-decarboxylase has recently been isolated in a highly purified form [34]. It requires pyridoxal phosphate as a cofactor as well as ionic iron. In the larva, dopamine *(4)* can only be detected under certain conditions; it is very rapidly acetylated with acetyl-coenzyme A as acetyl donor, and *N*-acetyldopamine

[31] *P. Karlson*, Hoppe-Seylers Z. physiol. Chem. *318*, 194 (1960).

[32] *P. Karlson* and *C. E. Sekeris*, Nature (London) *195*, 183 (1962).

[33] *C. E. Sekeris* and *P. Karlson*, Biochim. biophysica Acta *62*, 103 (1962).

[34] *C. E. Sekeris*, Hoppe-Seylers Z. physiol. Chem., in the press.

(5) is produced [35]. This can finally be oxidized in the cuticle to its quinone, which reacts with the proteins in a manner which has not yet been fully elucidated. Part of the *N*-acetyldopamine is apparently rendered inaccessible to this reaction by conversion into its glycoside [36]. Insects (in contrast to vertebrates) are well able to transform phenols and other substances into glycosides. Similar effects have been observed by *Brunet* and *Kent* [37] with protocatechic acid, as well as by *Butenandt* et al. [38] with the ommochromes.

There is also another metabolic path from tyrosine which passes through *p*-hydroxyphenylpyruvic acid *(6)* to *p*-hydroxyphenylpropionic acid. This involves a transamination, followed by a probably complex transformation in the side chain; for instance, it may involve reduction to the lactic acid derivative and then removal of water and reduction to the phenylpropionic acid derivative. (The latter reaction has its analogy in the synthesis of fatty acids.)

The following finding is of importance for determining the mode of ecdysone action: if ecdysone is injected, a rise in decarboxylase activity is observed (Fig. 4). We

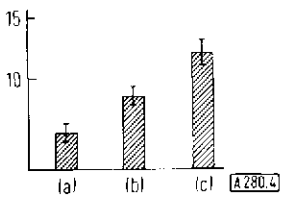


Fig. 4. Increase of dopa-decarboxylase activity following injection of (b) 2 and (c) 4 *Calliphora* units of ecdysone into *Calliphora* larvae; (a) is the control. The quantity of dihydroxyphenylalanine [% of initial amount] converted into dopamine serves as a measure of the enzymic activity. Data from [39].

Ordinate: enzymatic activity 10 hours after injection.

have evidence that new enzyme protein is formed during this rise [39,40]. We assume that action of ecdysone on the appropriate gene locus is the cause of this enzyme production (see above). In any case, the increase in enzymatic activity means that the second path of tyrosine catabolism is followed preferentially, as can be established from the metabolic products.

There is also a second enzyme of tyrosine metabolism which is controlled by ecdysone, *viz.* the activating enzyme of the phenol oxidase complex. *Horowitz* and *Fling* [41] have shown that the phenol oxidase of flies exists in an inactive form as a proenzyme; it is only through the action of an activator enzyme, which is also present in homogenates, that the proenzyme is converted into the active phenol oxidase.

We have studied this reaction more closely and found that several proteases also activate the proenzyme [42]. Attempts to concentrate the activator(s) and the proenzyme are in progress; up to the present, we have been able to purify and crystallize only the active phenol oxidase [43]. It should be termed an *o*-diphenol oxidase on account of its specificity; dopamine, *N*-acetyldopamine, and dopa have proved to be the best substrates. This incidently lends further support to our finding that *N*-acetyldopamine is the precursor of sclerotin.

We have investigated the action of ecdysone on the phenol oxidase system in view of the action of this hormone in sclerotization. It was found that the activator enzyme is controlled by the hormone. If the ring gland (the endocrine organ) is destroyed, the activity ceases; if ecdysone is injected, then the curve again rises steeply [44]. We have considered this effect to be also the result of the formation of new enzyme protein, which we interpret as being due to the influence of the hormone on certain genes.

In conclusion, it can be said that puparium formation by *Calliphora* larvae is a well investigated example of biochemical hormone action. It involves the shift of tyrosine metabolism in the direction of *N*-acetyldopamine formation; the latter was encountered as a new metabolite, which is oxidized in the cuticle (or in the epidermal cells) to give the quinone. This reacts immediately with the cuticular proteins to effect a kind of quinone tanning. The change in metabolism can be ascribed to the new synthesis of several enzymes; it is very probable that ecdysone activates certain gene loci, by which means the protein synthesis is stimulated.

7. The Juvenile Hormone

Biological experiments carried out between 1936 and 1940 [45,46] had already demonstrated the endocrine function of the corpora allata. Subsequent attempts to prepare an active extract of the hormone remained without success for a long time, presumably because initially no sensitive bioassay was available, and because the gland, which was mostly used as starting material, contains only little juvenile hormone. Starting from other observations, *Williams* found a plentiful source of the juvenile hormone in the posterior region of *Cecropia* moths (males) and a suitable assay organism in the diapausing pupa of *Cecropia*.

He then showed that with extracts it was far easier to obtain an effect on the pupa (changing the imaginal moulting into a second pupal moulting) than on the larva (changing a pupal moulting into a larval moulting), which had been used in the early transplantation experiments [47]. We therefore also used local formation of pupal cuticle in adult beetles as a biological reaction in the *Tenebrio* test which we developed [48] (cf. Fig. 5).

[35] *P. Karlson* and *H. Ammon*, Hoppe-Seylers Z. physiol. Chem., in the press.

[36] *P. Karlson, C. E. Sekeris*, and *K. E. Sekeri*, Hoppe-Seylers Z. physiol. Chem. *327*, 86 (1962).

[37] *P. C. I. Brunet* and *P. W. Kent*, Proc. Roy. Soc. (London) Ser. B *144*, 259 (1955).

[38] *A. Butenandt* and *W. Schäfer:* Venkataraman Jubilee Volume Academic Press, New York, London 1962; *H. Kübler*, Ph. D. thesis, Universität Tübingen, 1960.

[39] *P. Karlson* and *C. E. Sekeris*, Biochem. biophysica Acta *63*, 489 (1962).

[40] *C. E. Sekeris*, unpublished data.

[41] *N. H. Horowitz* and *M. Fling* in *W. D. McElroy* and *B. Glass*: Amino Acid Metabolism. Johns Hopkins University Press, Baltimore 1955, p. 219.

[42] *A. Schweiger* and *P. Karlson*, Hoppe-Seylers Z. physiol. Chem. *329*, 210 (1962).

[43] *P. Karlson* and *H. Liebau*, Hoppe-Seylers Z. physiol. Chem. *326*, 135 (1961).

[44] *P. Karlson* and *A. Schweiger*, Hoppe-Seylers Z. physiol. Chem. *322*, 199 (1961).

[45] *V. B. Wigglesworth*, Quart. J. microscop. Sci. *79*, 91 (1936).

[46] *J. J. Bounhiol*, Bull. biol. France Belgique Suppl. *24*, 1 (1938).

[47] *H. Piepho*, Roux' Archiv Entwicklungsmechan. Organismen *141*, 500 (1942).

[48] *P. Karlson* and *M. Nachtigall*, J. Insect Physiol. 7, 210 (1961).

Attempts at concentrating and isolating the juvenile hormone soon followed its first successful extraction [49, 50]. It has been mentioned at various times [49, 50] that highly concentrated extracts have been obtained,

Fig. 5. Action of juvenile hormone in the *Tenebrio* test. For this assay, young (24–48 hour old) pupae of the meal beetle *Tenebrio molitor* are used. They receive an injection of 0.5 µl of an oily solution of the test material into the abdomen. The beetles emerge 8–10 days after injection. If the substance was active, a region of pale pupal cuticle appears in the dark brown cuticle of the beetle. The test results are expressed as the percentage of positive animals (30–40 beetles per test); cf. Table 1.

but there is still no published account of a method with quantitative data. The juvenile hormone is said to be very sensitive when impurities (perhaps antioxidants?) have been removed during purification.

The juvenile hormone appears to be widely distributed. Active extracts have been obtained from various lepidopteran species. Numerous caterpillars and moths, even pupal extracts, possess a low activity; other insect orders and even microorganisms have also yielded active extracts [51]. It was surprising that vertebrate organs also appear to contain juvenile hormone. Adrenal cortex and thymus were especially active, but other organs gave inactive extracts [52]. This seems to open up a new approach for working up the much disputed thymus gland hormone. Nevertheless, the almost ubiquitous occurrence of active material as well as the activity of several common and comparatively simple substances (see below) suggest that probably it is a non-specific effect.

Nothing can yet be stated definitely about the chemical nature of the juvenile hormone. However, known compounds have recently been shown to possess the same action. Starting from the finding that *Tenebrio* faeces contain juvenile hormone [53], *Schmialek* detected farnesol and farnesal in the extract [54]. These compounds possess definite juvenile hormone activity. We then tested some other compounds (cf. Table 1). Farnesyl phosphate has only weak activity and the pyrophosphate is completely inactive. It is interesting that the methyl ether of farnesol and *N,N*-diethylfarnesylamine are especially active [56]. Whether this is because farnesol is rapidly degraded or metabolized in the organism, whereas the derivatives are more stable and can act for longer, is not yet clear.

Table 1. Action of several substances in the *Tenebrio* test [55].

Substance	Dose [µg/animal]	Activity in Tenebrio [%] [*]	TU/mg. [**]
Cecropin, oil extract	15	40	66
Farnesol	10	22	50
Farnesyl phosphate (suspension in oil)	50	66	(40)
Farnesyl pyrophosphate (suspension in oil)	50	0	0
(suspension in water)	50	0	0
Nerolidol	10	36	50
	50	73	
Squalene	50	3	1.5
Phytol	50	19	10
Citronellol	50	6	3
Geraniol	50	23	12
β-Ionone	50	4	2
Citral	50	0	0
Farnesyl methyl ether	0.1	40	10000
N,N-Diethylfarnesylamine	0.5	46	2300

[*] Number of animals [% of total treated] which form a pupal cuticle locally.
[**] 40 % positive animals = 1 TU (*Tenebrio* unit).

Thus, the question arises whether the juvenile hormone is to be identified with farnesol or its derivatives. In the case of farnesol, the answer is negative; the activity is too small; besides, the physical characteristics of juvenile hormone appear to be different from those of farnesol. For the methyl ether, the question cannot be finally answered. There is however much in favour of the view that the sesquiterpenes are to some extent master keys which happen to possess the same biological activity. There are very many such 'master keys' in the estrogen series; the best known is diethylstilbestrol.

Soon after publication of the results of *Clever* and *Karlson* [28] similar hypotheses [57] for the mode of action of juvenile hormone were expounded. However, no experiments to test them were reported.

8. Other Insect Hormones

There are still some further endocrine controls in the insect organism. These hormones are formed by neurosecretory cells and have attracted interest particularly in this context.

The diapause hormone of the silk moth [58] has been relatively well investigated, but not yet isolated in a pure form. *Hasegawa* [59] obtained the first active extracts in 1953. A pure preparation has not yet been reported.

The biological function of the diapause hormone consists of determining the embryonic development in the egg. The first summer generation of silk moths lays eggs which develop immediately; after a few weeks, the young larvae hatch out. They grow to form a second generation, whose eggs hiber-

[49] *C. M. Williams*, Nature (London) *178*, 212 (1956).
[50] *L. I. Gilbert* and *H. A. Schneiderman*, Science *128*, 844 (1958).
[51] *L. I. Gilbert* and *H. A. Schneiderman*, Amer. Zool. *1*, 11 (1961).
[52] *C. M. Williams*, *L. V. Moorhead*, and *J. F. Pulis*, Nature (London) *183*, 405 (1959).
[53] *P. Karlson* and *P. Schmialek*, Z. Naturforsch. *14b*, 12 (1959).
[54] *P. Schmialek*, Z. Naturforsch. *16b*, 461 (1961).
[55] *P. Karlson* and *H. Ehmke*, unpublished results; see also *P. Schmialek*, German Printed Patent Application 1140394 (Nov. 29th, 1962); *P. Karlson*: 13. Colloquium der deutschen Gesellschaft für physiologische Chemie. Springer Verlag, Berlin-Göttingen-Heidelberg 1963, p. 101.
[56] *V. B. Wigglesworth*, J. Insect Physiol., in the press.
[57] *C. M. Williams*, Science *133*, 1370 (1960).
[58] *S. Fukuda*, Proc. Japan Acad. *27*, 672 (1951); *29*, 389 (1953).
[59] *K. Hasegawa*, Nature (London) *179*, 1300 (1957).

nate; at a certain stage, embryonic development ceases in diapause and only begins again several months later. The temperature and length of day during larval development of the female are decisive for the character of her eggs. The regulation of diapause is monitored by a hormone formed in certain nerve centres, *viz.* the suboesophageal ganglion. Active extracts, which induce the female moth to lay winter eggs can be prepared from these cells.

What is even more astonishing than this complicated but biologically efficient mechanism is the fact that observations have been made according to which the endogenous rhythm is endocrine controlled and transferable [60]. The experimental animals were cockroaches which possess a day-night rhythm; by day they are immobile and remain in their hiding places, at night they run about. The cycle is maintained, even when the length of day (period of illumination) is altered. By transplantation of nervous tissue, a new rhythm can be imposed on experimental animals; the same effect can be achieved by injecting extracts.

Other materials activate the movements of certain organs (gut, Malpighian tubules, tubular heart). This mainly entails influencing smooth muscle. These substances are formed in certain nervous tissues. *Cameron* [61] has found a substance with the characteristics of an aminophenol; perhaps it is a catecholamine or a serotonin derivative. A similar material has been found in the nervous system of certain crabs [62]. This substance has since been identified by synthesis as 5,6-dihydroxytryptamine [63]

The neurohormones found by *Gersch* and co-workers [14] in the nerve cords of some insects belong to the above group. They likewise have a myotropic action; moreover, they influence the chromatophores. Quite recently, crystallization of some of these substances has been reported, but nothing is yet known of their chemical nature. The criteria of purity are not yet entirely satisfactory, although it must be admitted that it is difficult to produce unassailable criteria with such small amounts of material (50–100 μg).

9. Pheromones

Karlson and *Lüscher* [64] have classified as pheromones those substances which mediate a material communication between individuals of one species. Choice of this name is intended to differentiate this class of substances clearly from the hormones and thereby to oppose an undesirable widening of the concept "hormone" [65]. Strictly speaking, the pheromones have no place in this article, as they are not hormones. However, because the pheromones of insects have been well studied, they will be briefly mentioned here. For a more detailed account, reference should be made to the current review by *Stamm* [66].

The best known examples of pheromones are the sex attractants of moths, which are produced in the female in certain glands and which attract the male, often over considerable distances.

The first sex attractant of this type and therefore the first pheromone to be obtained in a chemically pure form was bombykol, the sex attractant of the silk moth, which was isolated by *Butenandt* and coworkers [67]. Over 500000 scent glands had to be processed in a lengthy purification to obtain 10 mg of a derivative of the scent in crystalline form.

A micromethod for oxidative cleavage specially worked out for these substances [68] led to the formula of a hexadecadienol, which was then confirmed by synthesis [69]. The sex attractant, named bombykol, is 10-*trans*-12-*cis*-hexadecadiene-1-ol *(8)*.

$$H_3C-(CH_2)_2-\underset{cis}{CH=CH}-\underset{trans}{CH=CH}-(CH_2)_9-OH \qquad (8)$$

Bombykol is one of the most active substances known. A glass rod moistened with a solution of 10^{-12} μg/ml still shows an attractant action. One can calculate that only a few molecules are sufficient to be detected by the antennae of the male and effect attraction.

Besides the sex scents, other pheromones include the queen substance of bees, which has recently been found to be Δ^2-9-oxodecen-1-oic acid [70], as well as the trail marking substances of ants, termites [71], and bees. We have reviewed the chemistry and biology of these substances elsewhere [72, 73]; cf. also [66].

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[60] *J. Harker*, Ann. Rev. Entomol. *6*, 131 (1961).
[61] *M. L. Cameron*, Nature (London) *172*, 349 (1953).
[62] *D. B. Carlisle*, Biochem. J. *63*, 328 (1956).
[63] *H. G. Schloßberger* and *H. Kuch*, Chem. Ber. *93*, 1318 (1960).
[64] *P. Karlson* and *M. Lüscher*, Naturwissenschaften *46*, 63 (1959).
[65] *A. Bethe*, Naturwissenschaften *20*, 177 (1932).
[66] *D. Stamm*, Dtsch. med. Wschr., in the press.
[67] *A. Butenandt*, *R. Beckmann*, *D. Stamm*, and *E. Hecker*, Z. Naturforsch. *14b*, 283 (1959).
[68] *A. Butenandt*, *D. Stamm*, and *E. Hecker*, Chem. Ber. *94*, 1931 (1961).
[69] *A. Butenandt* and *E. Hecker*, Angew. Chem. *73*, 349 (1961).
[70] *C. G. Butler*, *R. K. Callow*, and *N. C. Johnston*, Nature (London) *184*, 1871 (1959); *M. Barbier*, *E. Lederer*, *T. Reichstein*, and *O. Schindler*, Helv. chim. Acta *43*, 1682 (1960).
[71] *M. Lüscher*, Ann. N.Y. Acad. Sci. *89*, 549 (1960).
[72] *P. Karlson*, Ergebn. Biol. *22*, 212 (1960).
[73] *P. Karlson* and *A. Butenandt*, Ann. Rev. Entomol. *4*, 39 (1959).

Gas Chromatographic Investigation of Racemization during Peptide Synthesis [*]

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Respectfully dedicated to Prof. Dr. Adolf Butenandt on the occasion of his 60th birthday

It is shown that the methyl esters of many diastereoisomeric N-trifluoroacetyldipeptides can be separated by gas chromatography on Golay columns. This makes it possible for the first time to carry out accurate quantitative investigations of racemization occurring during peptide synthesis without resort to measurements of optical rotation or enzymatic cleavage, and without having to isolate the peptides. Some well-known methods of forming peptides were examined using the synthesis of the methyl ester of carbobenzoxy-L-valyl-L-valine as an example. The synthesis of the methyl ester of N-trifluoroacetyl-L-valyl-L-valine was investigated as a model for the linking of peptides. The influence on racemization of numerous factors was determined. General conclusions could be drawn regarding peptide synthesis.

Introduction

Ever since the preparation of long-chain peptides from optically active amino acids was initiated, the steric purity of the amino acids employed and the racemization occurring during synthesis have become of much greater importance than was previously the case. It has been calculated [1] that during the synthesis of a peptide containing one hundred amino acids, only 37% all-L-peptide arises, if the amino acids employed are only 99% sterically homogeneous.

Practically pure amino acids can be prepared, and those derivatives that are required for peptide synthesis can generally be purified by recrystallization. Racemization is therefore of decisive importance for the steric homogeneity of the peptide product.

Racemization can be detected physically or enzymatically. When applying these methods, it is important that no fractionation occurs or is undertaken following a peptide synthesis before the methods can be applied, otherwise false conclusions may be drawn. From this point of view, any methods that have hitherto been developed are generally unsatisfactory.

The following methods have been employed hitherto:

a) Determination of purity using optical rotation. – Measurements of optical rotation are subject to an average error of 2–3% [2]. Analytically pure substances that can be weighed out accurately are required. These are mostly crystalline compounds, and during their isolation, fractionation can take place.

b) Total hydrolysis with acid and examination of the isolated amino acids for steric homogeneity. – Since racemization occurs during acid hydrolysis [3], the results obtained are erroneous. Some correction can be applied by submitting the amino acids in the peptide under examination to analogous treatment with acid and then taking the observed degree of racemization into account [4].

c) Enzymatic procedures. – The use of enzymatic procedures is subject to certain restrictions [5]:

1. The enzyme must be sufficiently active towards the peptide under examination.

2. The peptide must be split stereospecifically.

3. It must be possible to demonstrate the presence of uncleaved peptide moieties with great sensitivity.

4. The enzyme must not be inhibited by the substrate, the products of hydrolysis, or impurities.

Incomplete cleavage can thus be due to causes other than the presence of diastereoisomers. Consequently, only purified peptides can be examined. Enzymatic methods are preeminently suitable for this purpose but not for examination of racemization occurring during peptide synthesis.

An interesting enzymatic procedure has been suggested by *Greenstein* and coworkers: an aminopeptidase from kidney is employed that also hydrolyses diastereoisomeric peptides, and the D-amino acids are oxidized with D-amino acid oxidase.

d) Special methods. – *Young* and coworkers [6] have examined the racemization occurring during the synthesis of the ethyl ester of *N*-acetyl-L-leucyl-glycine by a variety of methods. The degree of racemization was determined by means of optical rotation, infrared spectra, and melting points. The products, which in the main were oils, rendered accurate investigation more difficult.

Anderson and *Callahan* [7] have found that the ethyl ester of carbobenzoxyglycyl-L-phenylalanylglycine can be separated from the DL-compound by fractional crystallization from a 2% ethanol solution, the racemate precipitating first under these conditions. It is worthy of note that crude products can clearly be employed also. For evaluation, however, both fractions must be crystallized out completely.

[*] Presented in brief at the Fifth European Peptide Symposium in Oxford, England, in September, 1962.

[1] *J. P. Greenstein* and *M. Winitz:* Chemistry of the Amino Acids. Wiley, New York 1961, p. 946.

[2] Cf. [1] p. 947.

[3] *A. Neuberger*, Advances Protein Chem. *4*, 339 (1948).

[4] *B. Riniker* and *R. Schwyzer*, Helv. chim. Acta *44*, 658 (1961).

[5] Cf. [1] p. 1254.

[6] *N. B. North* and *G. T. Young*, Chem. and Ind. *1955*, 1597; *N. A. Smart, G. T. Young*, and *M. W. Williams*, J. chem. Soc. (London) *1960*, 3902.

[7] *G. W. Anderson* and *F. M. Callahan*, J. Amer. chem. Soc. *80*, 2902 (1958).

According to a procedure of *Kenner* and coworkers [8], the synthesis of carbobenzoxyglycyl-L-alanyl-L-phenylalanylglycine from carbobenzoxy-glycyl-L-alanine and L-phenylalanylglycine or its methyl ester is investigated. The diastereoisomers are separated by multiplicative distribution. It sometimes happens that complete separation does not take place; the rotation of the DL-fraction must then be checked. Small quantities can only be estimated approximately.

e) Chromatographic procedures. – Some diastereoisomeric peptides can be separated by paper chromatography [4,9].

Separation of Diastereoisomeric N-Trifluoroacetyldipeptides as their Methyl Esters by Gas Chromatography

It was during gas chromatographic analysis of *N*-TFA-dipeptides as their methyl esters [*] on a column only 2 m long [10–12] that we first managed to separate two diastereoisomeric dipeptide derivatives, *viz.* the methyl esters of *N*-TFA-L-alanyl-L-phenylalanine and of *N*-TFA-L-alanyl-D-phenylalanine [10]. Since then, we have succeeded in separating further diastereoisomeric *N*-TFA-dipeptides as their methyl esters on capillary columns of the *Golay* type. In this work, two steel columns, each 50 m long, were used; one was coated with polypropylene glycol (Perkin-Elmer R column) and the other with polyphenyl ether (Perkin-Elmer OS 138 column). Table 1 shows the *N*-TFA-dipeptides that have so far been examined and separated as their methyl esters, together with the experimental conditions.

Table 1. Gas chromatographic separation of diastereoisomeric *N*-trifluoroacetyldipeptides in the form of their methyl esters on capillary columns. Nitrogen was used as carrier gas and methyl myristate (C_{14}) as reference substance in all measurements.

Peptide	Capillary column [a]	Sepn. temp. [°C]	Flow rate [f] [Nml/min]	Total retention C_{14} [min]	q_G [b] L,L	q_G [b] D,L	Resolution [%]
Ala-Ala	R	180	2.19	25.13	0.92	0.86	93
Ala-Val	R	180	2.19	25.44	1.07	1.12	78
Ala-Leu	R	180	2.19	25.25	1.62	1.67	59
Ala-Phe	OS	221	1.62	9.38	5.16	5.84	99
Ala-Met	OS	221	1.62	8.94	3.55	3.72	51
Ala-But [c]	OS	184	0.70	39.50	0.72	—	shoulder
Val-Val	R	180	2.19	25.00	1.07	1.19	98
Val-Leu	R	180	2.19	24.88	1.64	1.77	87
Val-Phe	OS	221	1.62	8.88	5.37	6.11	100
Val-Met	OS	221	1.62	8.88	3.79	3.94	74
Leu-Val	R	180	2.19	25.13	1.45	1.58	99
Leu-Leu	R	180	2.19	25.19	2.14	2.29	92
Leu-Ileu	R	180	2.19	25.00	1.99	2.19	96
Leu-Met	OS	221	1.62	9.06	4.58	4.77	60
Leu-Pro	R	180	2.19	25.00	2.58	2.64	69
Leu-Phe	OS	221	1.62	9.44	6.39	7.20	99
Ileu-Val	OS	185	0.70	38.88	0.98	1.04	93
Pro-Val	OS	192	0.68	18.00	2.19	2.74	100
Met-Ala	OS	221	1.62	8.81	2.78	2.84	10
Met-Val	OS	221	1.62	8.88	3.15	3.41	93
Phe-Ala	OS	221	1.62	8.88	4.10	4.32	88
Phe-Val	OS	221	1.62	9.31	4.96	5.42	98
Phe-Leu	OS	221	1.62	9.29	6.55	6.78	70
Phe-But [c]	OS	221	1.62	8.81	4.79	5.18	96
Glu-α-Ala	OS	221	1.62	8.94	2.50	2.55	46
Glu-α-Val	OS	221	1.62	8.88	2.80	3.01	96
Glu-α-Leu	OS	221	1.62	8.75	3.82	3.92	79
Glu-α-Ileu	OS	221	1.62	8.88	3.70	3.96	94
Glu-γ-Ala [d]	OS	221	1.62	8.94	— 4.35 —		14
Glu-γ-Val [d]	OS	221	1.62	8.88	— 5.23 —		17
Glu-γ-Leu [d]	OS	221	1.62	8.75	— 7.36 —		shoulder
Glu-γ-Ileu [d]	OS	221	1.62	8.88	— 7.04 —		6
Ser-Leu [e]	OS	184	0.70	38.88	1.19	1.23	87
But-Val [c]	OS	193	0.68	34.69	0.83	0.90	97

[a] R = steel column 50 m long coated with polypropylene glycol (Perkin-Elmer R column) OS = steel column 50 m long coated with polyphenyl ether (Perkin-Elmer OS 138 column).
[b] q_G is the total retention of the diastereoisomers relative to the total retention of the reference substance = 1.00. On account of the asymmetry of the peaks (see Fig. 2), the total retentions were determined from the peak origins.
[c] But = α-aminobutyric acid. These compounds were obtained from methionine dipeptides by desulfurization with Raney nickel [12].
[d] Allocation of the peaks has not yet been possible with those compounds.
[e] Examined as *N*-TFA-(*O*-trimethylsilyl)-ser-leu-OCH_3 [12].
[f] Nml = ml at normal pressure and temperature.

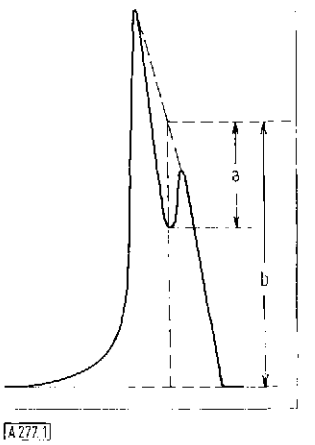


Fig. 1. Graphic determination of the resolution δ = a/b [%].
Ordinate: Quantity of substance
Abscissa: Time

The degree of separation is characterized by the resolution δ [13] (cf. Fig. 1). It follows from the relationship between resolution and overlapping of material (Table 2)

Table 2. Relationship between resolution and overlapping of material

Resolution δ [%]	Overlapping of material [%]
50	12.5
80	3.2
90	0.9
99	0.0001

[14] which is, of course, only valid for ideal Gaussian distribution curves, that with 90% resolution, for example, 0.9% of the incompletely separated second component is no longer discernible. Therefore, for quantitative investigations of racemization during peptide synthesis, only separations giving a resolution greater than 90% are useful, if less than 1% of the diastereoisomeric compound is to be detected. Tailing is detrimental to the resolution, but this has been taken into account in Table 1. The resolution of the compounds

[8] *D. W. Clayton, J. A. Farrington, G. W. Kenner*, and *J. M. Turner*, J. chem. Soc. (London) *1957*, 1398.

[9] *J. W. Hinman, E. L. Caron*, and *H. N. Christensen*, J. Amer. chem. Soc. *72*, 1620 (1950); *E. Taschner*, Lecture delivered at the 5th European Peptide Symposium, Oxford 1962.

[*] TFA = trifluoroacetyl.

[10] *F. Weygand, B. Kolb, A. Prox, M. A. Tilak*, and *I. Tomida*, Hoppe-Seylers Z. physiol. Chem. *322*, 38 (1960).

[11] *F. Weygand, B. Kolb*, and *P. Kirchner*, Z. analyt. Chem. *181*, 396 (1961).

[12] *F. Weygand, A. Prox, E. C. Jorgensen, R. Axén*, and *P. Kirchner*, Z. Naturforsch., in the press.

[13] *R. Kaiser*: Chromatographie in der Gasphase. Bibliographisches Institut, Mannheim 1961, Vol. 1, p. 51.

[14] Cf. [13] p. 53, from which Table 2 is reproduced.

listed in Table 1 can doubtlessly be improved further by altering the gas chromatographic conditions.

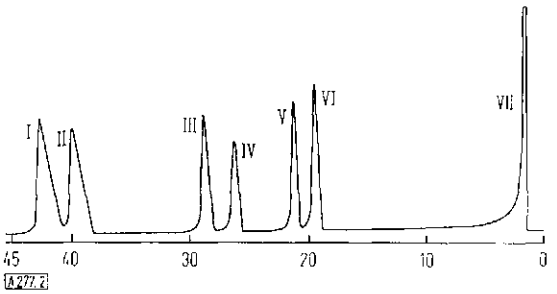


Fig. 2. Gas chromatographic separation of diastereoisomeric *N*-trifluoroacetyldipeptides as their methyl esters.
Steel column (50 m), coated with polypropylene glycol (Golay column R of Perkin-Elmer). Carrier gas: nitrogen.
Separation temperature: 180 °C. Flow rate: 2.19 Nml/min.
I = *N*-TFA-L-leu-D-leu-OCH_3 II = *N*-TFA-L-leu-L-leu-OCH_3
III = *N*-TFA-L-leu-D-val-OCH_3 IV = *N*-TFA-L-leu-L-val-OCH_3
V = *N*-TFA-L-val-D-val-OCH_3 VI = *N*-TFA-L-val-L-val-OCH_3
VII = Ethyl acetate

Fig. 2 gives examples of the separation of diastereoisomers on an R column. The compounds were injected simultaneously in ethyl acetate.

Investigations of Racemization

General

The separation of diastereoisomers by gas chromatography has until now been restricted to peptides containing only two optically active amino acids. Tripeptides have not yet been examined. L,L- and D,D-compounds on the one band, and L,D- and D,L-compounds on the other, cannot be distinguished. For this reason, it is impossible to decide which of two amino acids racemizes during peptide synthesis. When amino acid esters are used for dipeptide syntheses however, it can be assumed that mainly the *N*-terminal, activated amino acid racemizes. Observations to the contrary have not been made.

The advantages of gas chromatography are significant. Diastereoisomeric methyl esters of *N*-TFA-dipeptides are separated independent of any solvents, untransformed reagents, by-products, additions, and other impurities. Furthermore, the sensitivity of the process exceeds that of all other methods hitherto employed. At high resolution, a diastereoisomer content of less than 1 % can still be determined quantitatively.

Racemization occurring during peptide synthesis with various methods can therefore be observed; the influence on racemization of inductive and steric effects, changes of temperature, solvents, and additions such as salts and tertiary bases can be rapidly determined.

Only the methyl esters of *N*-trifluoroacetyldipeptides can be separated. However, if other amino-protecting groups can be replaced by the trifluoroacetyl residue after completion of a peptide synthesis, without fractionation or racemization occurring, then the method is of general applicability. It is clear from the results to be discussed in greater detail below that no racemization occurs during replacement of a carbobenzoxy residue by a trifluoroacetyl residue.

As a result of the strong inductive effect of the CF_3 group, it appears that during the synthesis of methyl esters of *N*-TFA-dipeptides, racemization occurs to an extent at least as large as that occurring during the combination of *N*-acyl-dipeptides with peptide or amino acid esters [4,6,15–23].

The gas chromatograms were evaluated by integration of the peaks. Using some experimental mixtures prepared from pure components, it was demonstrated that there is a practically linear relationship between the areas under the peaks and the composition of the mixtures. The experimental mixtures consisted of the methyl esters of *N*-TFA-L-valyl-L-valine and *N*-TFA-L-valyl-D-valine and of the methyl esters of a diastereoisomeric pair of *N*-TFA-leucylvaline. With each mixture, exact correspondence was found between the ratio of the areas under the peaks and the ratio of the weights of the components. A flame-ionisation detector was used for the measurements.

Consequently, the percentage of diastereoisomeric compound in the total amount of peptide is determined. The degree of racemization is obtained by doubling this value. The mean error of a single measurement is ± 0.4 %. During the gas chromatographic investigations no thermal racemization occurs.

Results

Up to the present time, the following procedures for the preparation of peptide bonds have been examined:

1. Activated ester method (*p*-nitrophenyl esters [24], cyanomethyl esters [25,26], thiophenyl esters in glacial acetic acid [27], and vinyl esters [28]).
2. Dicyclohexylcarbodiimide method [29].
3. Azide method [30].
4. Carbonyldiimidazole method [16b].

[15] *J. R. Vaughan, Jr.*, J. Amer. chem. Soc. *74*, 6137 (1952).
[16] [a] *G. W. Anderson, J. Blodinger*, and *A. D. Welcher*, J. Amer. chem. Soc. *74*, 5309 (1952); [b] *G. W. Anderson* and *R. Paul*, ibid. *80*, 4423 (1958).
[17] *J. A. Farrington, P. J. Hextall, G. W. Kenner*, and *J. M. Turner*, J. chem. Soc. (London) *1957*, 1407.
[18] *K. Hofmann, M. E. Woolner, G. Spühler*, and *E. T. Schwartz*, J. Amer. chem. Soc. *80*, 1486 (1958).
[19] *W. Grassmann, E. Wünsch*, and *A. Riedel*, Chem. Ber. *91*, 455 (1958).
[20] *R. Schwyzer, B. Iselin, H. Kappeler, B. Riniker, W. Rittel*, and *H. Zuber*, Helv. chim. Acta *41*, 1287 (1958).
[21] *H. Schwarz* and *F. M. Bumpus*, J. Amer. chem. Soc. *81*, 890 (1959).
[22] *R. Schwyzer* and *B. Iselin*, Helv. chim. Acta *43*, 1760 (1960).
[23] *K. Lübke* and *E. Schröder*, Z. Naturforsch. *16b*, 765 (1961).
[24] *M. Bodanszky*, Nature (London) *175*, 685 (1955).
[25] *R. Schwyzer* et al., Helv. chim. Acta *38*, 69, 80, 83 (1955).
[26] *F. Weygand* and *W. Swodenk*, Chem. Ber. *90*, 639 (1960).
[27] *F. Weygand* and *W. Steglich*, Chem. Ber. *93*, 2983 (1960).
[28] *F. Weygand* and *W. Steglich*, Angew. Chem. *73*, 99 (1961).
[29] *J. P. Sheehan* and *G. P. Hess*, J. Amer. chem. Soc. *77*, 1067 (1955).
[30] *T. Curtius*, Ber. dtsch. chem. Ges. *35*, 3226 (1902); *J. I. Harris* and *T. S. Work*, Biochem. J. *46*, 582 (1950); *N. A. Nyman* and *R. M. Herbst*, J. org. Chemistry *15*, 108 (1950).

5. Phosphorazo method [31].
6. Mixed anhydride method [32].
7. *Woodward*'s method [33].
8. *Patchornik*'s method [34].

In performing these syntheses, we strictly followed the procedures given in the original communications. Details are noted in the tables.

We concentrated our attention first on a study of the synthesis of valylvaline, since here the steric effect caused by the two isopropyl side chains should be of great influence. L-Valine from the same batch was used for all experiments. Since no racemization was observed in some syntheses, this L-valine must also have been free from racemate. When the degree of racemization is given as less than 2 % in the tables, this means that no signal for *N*-TFA-D-val-L-val-L-val-OCH_3 could be observed under the conditions of the experiment.

a) *Methyl Ester of Carbobenzoxyvalylvaline*

The methyl ester of carbobenzoxy-L-valyl-L-valine was treated in the following manner: After distilling off the readily volatile solvent *in vacuo*, the residue was taken up in ethyl acetate and the solution was washed in turn with sodium bicarbonate solution, dilute hydrochloric acid, and water, and then finally dried over sodium sulfate. After distilling off the ethyl acetate *in vacuo*, the carbobenzoxy residue was removed by heating with anhydrous trifluoroacetic acid [35]. Subsequently, the trifluoroacetic acid was distilled off, and the trifluoroacetyl residue introduced with methyl trifluoroacetate in the presence of triethylamine [36]. The readily volatile reagents were distilled off *in vacuo*, and the residue dissolved in ethyl acetate and washed with dilute hydrochloric acid and water. After drying with sodium sulfate, the solution was injected into the gas chromatograph. The yield was not determined in any experiment.

No racemization occurs in the synthesis of the methyl ester of carbobenzoxy-L-valyl-L-valine by most methods. It is immaterial whether the free methyl ester of valine is used, or whether this compound is first liberated in the solvent with triethylamine from its hydrochloride. Only in the case of the cyanomethyl ester method did we find a racemization of 2 % (8 hours at 110 °C in ethyl acetate). If heated for only 2 hours [25] no peptide formed, which is indicative of the reaction-retarding influence of the isopropyl groups. We also found racemization, amounting to 29 %, in the reaction of the thiophenyl ester of carbobenzoxy-L-valine with free L-valine in glacial acetic acid. We had previously found [27] (although by the methods used at that time) that no racemization takes place during peptide synthesis from the thiophenyl esters of carbobenzoxyamino acids and free amino acids in glacial acetic acid, if the amino acids used had little steric hindrance.

b) *Methyl Ester of N-Trifluoroacetylvalylvaline*

The results obtained in the synthesis of the methyl ester of *N*-trifluoroacetyl-L-valyl-L-valine are quite different (Table 3). Only syntheses by the azide method

Table 3. Racemization occuring during the preparation of *N*-TFA-L-val-L-val-OCH_3

Method	Free ester	Ester·HCl + $N(C_2H_5)_3$	Solvent	Temp. [°C]	Time [h]	Degree of racemization [%]
Activated ester						
O-vinyl	+	–	Diethyl malonate	+24	72	<2
O-vinyl	+	–	Ethyl cyanoacetate	+100	2	<2
O–CH_2CN	+	–	Ethyl acetate	+24	48	[b]
O–CH_2CN	+	–	Ethyl acetate	+110 (bath)	2	[c]
O–CH_2CN	+	–	Ethyl acetate	+110 (bath)	13	16.8
O–CH_2CN	–	+	Ethyl acetate	+110 (bath)	8	21.6
S–C_6H_5	free amino acid		Glacial acetic acid	+130 (bath)	2	38.6
Dicyclohexylcarbodiimide	+	–	CH_2Cl_2	−10	72	2.4
	+	–	CH_2Cl_2	+24	72	7.2
	–	+	CH_2Cl_2	−10	48	18.4
	–	+	CH_2Cl_2	+24	48	42.0
Azide [a]	+	–	Ethyl acetate	−10	43	<2
	–	+	Ethyl acetate	−10	42	<2
Carbonyldiimidazole	+	–	THF [d]	−10	19	19.4
	+	–	THF	+24	23	90.8
	–	+	THF	+24	22	90.2
Woodward	+	–	CH_3CN	+24	13	69.4
Patchornik *N*-Bromosuccinimide	–	+	DMF [e]	0	7 min	23.4

[a] Prepared from recrystallized *N*-TFA-L-val-NHNH-trityl.
[b] No peptide.
[c] Very little peptide.
[d] THF = tetrahydrofuran.
[e] DMF = dimethyl formamide.

or by the vinyl ester method proceed without racemization [37]. Racemization in the other processes depends on the solvent, the reaction temperature and the method used to introduce the methyl ester of L-valine. Racemization is less when the free ester is added than when it is liberated in the solvent from its hydrochloride with triethylamine. In the latter case, a portion of the triethylamine hydrochloride, depending on the solvent, always remains in solution.

[31] *S. Goldschmidt* and *H. Lautenschläger*, Liebigs Ann. Chem. *580*, 68 (1953).

[32] *T. Wieland* and *R. Sehring*, Liebigs Ann. Chem. *569*, 122 (1950); *R. A. Boissonnas*, Helv. chim. Acta *34*, 874 (1951); *J. R. Vaughan, Jr.*, J. Amer. chem. Soc. *73*, 3547 (1951); *T. Wieland* and *H. Bernhard*, Liebigs Ann. Chem. *572*, 190 (1951).

[33] *R. B. Woodward, R. A. Olofson*, and *H. Meyer*, J. Amer. chem. Soc. *83*, 1010 (1961).

[34] *Y. Wolma, P. M. Gallop*, and *A. Patchornik*, J. Amer. chem. Soc. *83*, 1263 (1961).

[35] *F. Weygand* and *W. Steglich*, Z. Naturforsch. *14b*, 472 (1959).

[36] *F. Weygand* and *R. Geiger*, Chem. Ber. *92*, 2099 (1959).

[37] The *p*-nitrophenyl ester and the phosphorazo methods have not yet been investigated. The method of mixed anhydrides is not applicable, as it was known that 2-trifluoromethyloxazol-5-ones are readily formed in this process [*F. Weygand, W. Steglich*, and *H. Tanner*, Liebigs Ann. Chem. *658*, 128 (1962)]. According to more recent unpublished experiments (N. M. R. spectra) carried out in conjunction with *W. v. Philipsborn* and *D. Mayer*, these compounds are present in the pseudooxazolone form.

The factors that are of importance for racemization were examined using the dicyclohexylcarbodiimide method. It can be seen from Table 4 that the degree of racemization increases markedly with rise of temperature

Table 4. Influence of temperature on racemization during the synthesis of *N*-TFA-L-val-L-val-OCH_3 with dicyclohexylcarbodiimide. Solvent: dichloromethane

Free ester	Ester·HCl + 0.9 equiv. of Et_3N [*]	Temp. [°C]	Additions	Time [h]	Degree of racemization [%]
+	–	−10	–	72	2.4
+	–	+24	–	72	7.2
+	–	−10	100 mole-% Et_3N·HCl [*]	48	5.2
+	–	+24	100 mole-% Et_3N·HCl [*]	41	68.0
–	+	−10	–	48	<2
–	+	+24	–	41	43.6

[*] Et_3N = triethylamine.

Table 5. Influence of triethylamine on racemization during the synthesis of *N*-TFA-L-val-L-val-OCH_3 with dicyclohexylcarbodiimide. The free ester was used for the synthesis

Solvent	Temp. [°C]	Triethylamine [mole-%]	Time [h]	Degree of racemization [%]
CH_2Cl_2	+ 24	10	41	22.0
CH_2Cl_2	+ 24	30	47.5	38.4
CH_2Cl_2	+ 24	50	47.5	63.6
CH_2Cl_2	+ 24	100	70	89.8
CH_2Cl_2	− 10	10	48	3.8
THF [*]	− 10	10	90	3.6
THF	+ 24	10	24	17.0

[*] THF = tetrahydrofuran.

Table 6. Influence of salts on racemization during the synthesis of *N*-TFA-L-val-L-val-OCH_3 with dicyclohexylcarbodiimide. The free ester was used for the synthesis.

Solvent	Temp. [°C]	Salt [*] [mole-%]	Time [h]	Degree of racemization [%]
CH_2Cl_2	+ 24	10 Et_3N·HCl	47	10.6
CH_2Cl_2	+ 24	50 Et_3N·HCl	47	35.4
CH_2Cl_2	+ 24	100 Et_3N·HCl	41	68.0
CH_2Cl_2	− 10	100 Et_3N·HCl	48	5.2
THF	− 10	100 Et_3N·HCl	90	4.4
THF	+ 24	100 Et_3N·HCl	24	8.8
CH_2Cl_2	+ 24	100 Et_3N·Ac	70	83.0
CH_2Cl_2	+ 24	100 Py·HCl	70	36.4
CH_2Cl_2	+ 24	100 Ester·HCl	67	13.4
THF	+ 24	100 LiBr	68	26.6
CH_2Cl_2	+ 24	[**]	69	12.4

[*] Et_3N·HCl = triethylamine hydrochloride.
Et_3N·Ac = triethylamine acetate.
Py·HCl = pyridine hydrochloride.
Ester·HCl = hydrochloride of L-val-OCH_3.
[**] Addition of 100 mole-% *N*-TFA-L-val + 100 mole-% L-val-OCH_3.

from −10 to +24 °C. Addition of triethylamine (Table 5) also produces a very significant increase in the degree of racemization. Triethylamine hydrochloride also effects rapid racemization depending on its concentration (Table 6). The degree of racemization in methylene chloride and tetrahydrofuran is small only when the temperature is low and the ester is liberated from its hydrochloride with triethylamine. Other salts, too, such as triethylammonium acetate [38] or pyridine hydrochloride in methylene chloride, or lithium bromide in tetrahydrofuran, considerably catalyse racemization. In contrast, the methyl ester of L-valine hydrochloride brings about an approximately two-fold increase in racemization.

Table 7. Influence of solvent on racemization during the synthesis of *N*-TFA-L-val-L-val-OCH_3 with dicyclohexylcarbodiimide

Free ester	Ester·HCl + 0.9 equiv. of Et_3N [a]	Solvent [b]	Addition [mole-%]	Time [h]	Degree of racemization [%]
Temperature: −10 °C					
+	–	CH_2Cl_2	10 Et_3N [a]	48	3.8
+	–	CH_2Cl_2	100 Et_3N·HCl[c]	48	5.2
–	+	CH_2Cl_2	–	48	<2
+	–	THF	10 Et_3N	90	3.6
+	–	THF	100 Et_3N·HCl	90	4.4
–	+	THF	–	90	<2(1.8)
Temperature: +24 °C					
+	–	CH_2Cl_2	10 Et_3N	41	22.0
+	–	CH_2Cl_2	100 Et_3N·HCl	41	68.0
–	+	CH_2Cl_2	–	41	43.6
+	–	THF	10 Et_3N	24	17.0
+	–	THF	100 Et_3N·HCl	24	8.8
–	+	THF	–	24	19.0
+	–	DMF	–	70	53.4
+	–	DMF	10 Et_3N	90	59.4
+	–	DMF	100 Et_3N·HCl	91	62.6
–	+	DMF	–	91	58.8

[a] Et_3N = triethylamine.
[b] THF = tetrahydrofuran, DMF = dimethyl formamide.
[c] Et_3N·HCl = triethylamine hydrochloride.

Table 7 shows that in dimethyl formamide, which is frequently employed, extensive racemization occurs at 24 °C. The dicyclohexylurea formed remains in solution.

With increasing reaction time, the degree of racemization increases only slightly. If free L-valine-OCH_3 is the starting material, and the reaction is carried out in methylene chloride at 24 °C, 100 mole-% triethylamine hydrochloride being added to the mixture, then the degree of racemization is 56.0 % after 24 h, 57.2 % after 48 h, and 61.8 % after 96 h.

Since extensive racemization was observed with the carbonyldiimidazole method, we examined the effect of additions of imidazole or *N*-benzylimidazole on the results of the dicyclohexylcarbodiimide method. In both cases, the degree of racemization was about 80 %. Addition of water to the solvent (tetrahydrofuran) effected strong racemization (55.8 %).

We assume that racemization during peptide synthesis by the dicyclohexylcarbodiimide method is due in the main to the formation of oxazolone intermediates, which racemize very quickly. One can in fact demonstrate the presence of 2-trifluoromethyl-4-isopropyl-pseudooxazol-5-one *(1)* as an intermediate in the reaction of *N*-TFA-L-valine with the methyl ester of L-valine and dicyclohexylcarbodiimide in absolute tetrahydrofuran at 20 °C (Fig. 3). The pseudooxazolone, which is rapidly formed, reacts with the methyl ester of valine to yield the methyl ester of *N*-TFA-DL-valyl-L-

[38] The methyl ester of *N*-acetylvaline also appeared in this experiment.

valine [39]. It disappears, therefore, with increasing reaction time. The reaction of distilled 2-trifluoromethyl-4-isopropylpseudooxazol-5-one *(I)* (prepared from D,L-valine) with the methyl ester of L-valine in absolute

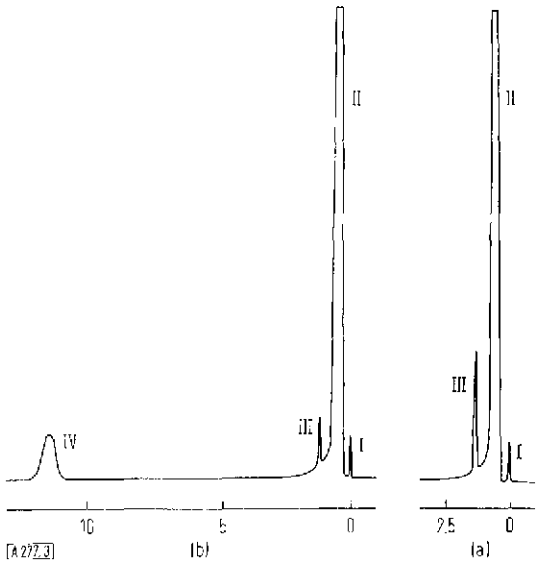
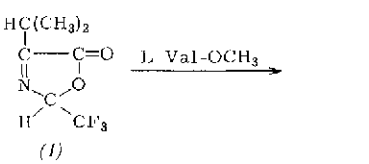
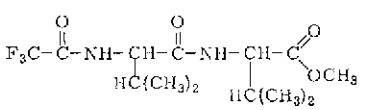


Fig. 3. Gaschromatographic demonstration of the formation of oxazolone during the synthesis of *N*-TFA-val-val-OCH_3 by the dicyclohexylcarbodiimide method. a) Reaction time: 30 min. b) Reaction time: 75 min.
Reaction conditions: 10^{-3} mole each of *N*-TFA-L-val-OH, L-val-OCH_3, and dicyclohexylcarbodiimide were mixed together in 1 ml of anhydrous tetrahydrofuran at 20 °C.
Gas chromatography: samples (2 µl) were separated on packed columns, 2 m long and coated with silicone grease, at 172 °C with 30 Nml of helium/min.
I = air.
II = tetrahydrofuran
III = 2-trifluoromethyl-4-isopropylpseudooxazol-5-one.
IV = methyl caprate as reference substance.

tetrahydrofuran at 20 °C yields 74 % L,L- and 26 % D,L-*N*-TFA-dipeptide as their methyl esters, as was shown by gas chromatography.



(I)



Conclusions

The results presented here confirm and extend previous knowledge of racemization occurring during peptide synthesis. The danger of racemization is least when *N*-acylamino acids with protecting groups of the urethane type (carbobenzoxy group) are employed. Syntheses *via* azides by the method of *Curtius* proceed without racemization, since in the synthesis of *N*-trifluoroacetyl-dipeptide esters no racemization was observed either. The vinyl ester method is equally satisfactory. However, vinyl esters are still not easy to prepare from peptides.

In all the other methods that start with *N*-acylpeptides, racemization is to be expected. For this reason, these methods should not be used for the synthesis of peptides, since the exclusion of salts of all kinds, strong bases, and polar solvents is absolutely essential.

The results of the addition of imidazole or *N*-benzylimidazole in the dicyclohexylcarbodiimide method yield information that is of importance for the synthesis of sequences containing histidine. *K. Hofmann* and co-workers [18] had already observed racemization in the arginine portion of a peptide synthetized from carbobenzoxy-L-his-L-phe-L-nitroarg-OH and L-tyr-gly-O-benzyl in the presence of dicyclohexylcarbodiimide. Similarly, in the reaction of carbobenzoxy-L-val-L-tyr-OH with L-val-L-his-L-pro-L-phe-OCH_3 *Riniker* and *Schwyzer* [4] observed about 30 % racemization in the tyrosine part of the hexapeptide. In our opinion, these instances of racemization can be attributed to the presence of histidine, since we observed a vast increase in racemization when imidazole or *N*-benzylimidazole was added. Sequences containing histidine should therefore only be prepared by way of acylamino acids with urethane structures, or else from *N*-acylpeptides by the azide method.

These restrictions are naturally not valid when glycine is in the *C*-terminal position. The behaviour of *C*-terminal proline or *N*-methylamino acids, in which oxazolone formation is not possible, has still to be investigated. Similarly, studies with tosyl- or phthalyl-amino acids have not yet been carried out.

Further studies should clarify the influence of the side chains of *N*-terminal amino acids on the synthesis of methyl esters of *N*-TFA-dipeptides. This is particularly so with amino acids, such as phenylalanine and tyrosine, which are sensitive to racemization [4, 21, 40]. It should also be possible to investigate by gas chromatography the racemization occurring during the combination of *N*-acylpeptides with peptide esters, if partial hydrolysis with 5 to 6 N HCl to the dipeptides proceeds without racemization. Hitherto we have only subjected carbobenzoxy-gly-L-ala-L-phe-gly-OCH_3 to partial hydrolysis. By less than 90 % resolution, only *N*-TFA-L-ala-L-phe-OCH_3 and no diastereoisomeric peptide was found in the hydrolysate, after esterification in methanol/HCl and trifluoroacetylation. In this connection, it is still an open question whether D-amino acids occurring in peptides can be detected in the form of methyl esters of *N*-TFA-dipeptides by gas chromatography.

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[39] *F. Weygand* and *U. Glöckler*, Chem. Ber. *89*, 653 (1956); *F. Weygand, W. Steglich*, and *H. Tanner*, Liebigs Ann. Chem. *658*, 128 (1962).

[40] *B. Iselin* and *R. Schwyzer*, Helv. chim. Acta *43*, 1760 (1960); Racemization during the preparation of carbobenzoxy-L-val-L-tyr-O-[*p*-NO_2-C_6H_4].

Fast Gas Reactions in Shock Waves and Detonations

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Shock waves provide a simple means of achieving high temperatures and hence of studying the kinetics of endothermal processes, e.g. dissociation reactions, above 1000 °K. Detonations can also be used for this purpose, but are restricted to a few exothermal mixtures. The production and properties of shock waves and detonations and the most important analytical methods used for kinetic investigations are described, and some typical results are discussed.

I. Introduction. Formulation of the Problem

Recently, one of the authors [1] presented a discussion of the problems of kinetics of gas reactions. There is a large class of gas reactions, especially chain reactions and reactions involving chain branching [*], investigation of which by classical methods, without disturbing the system, is extremely difficult and occasionally impossible. This is true of reactions that are proceeding only in temperature and pressure regions for which suitable reaction vessels and measurement techniques are lacking. Reactions which are strongly affected by the walls of the vessel in a manner that is poorly reproducible are difficult to study [*].

An observable or even strong influence of the vessel walls on the course of a reaction is always possible if the diffusion time is less than or equal to the reaction time. As reaction time we may choose the half-life of a reaction, and the diffusion time is the time that a particle requires to diffuse from the interior of the vessel to the wall. The diffusion coefficient of average gas molecules lies in the range of 1 cm^2/sec at temperatures of a few hundred degrees centigrade and atmospheric pressure; at lower pressure, it is correspondingly larger. With a vessel radius of 2 cm, a mean diffusion time $\tau \approx r^2/2\,D \approx 2$ sec is obtained. In a classical experimental setup, a comparable time is needed for filling the vessel and equilibration of the temperature. Therefore, the prerequisites for wall effects are nearly always existent.

Shock-wave technique is not the only method that permits measurements to be carried out practically without wall effects at short reaction times. A well-

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[1] *W. Jost*, Naturwissenschaften, in the press.

[*] Since the advent of uranium fission, chain reactions have become fashionable, and an extensive confusion of concepts has arisen. Therefore, some explanatory remarks seem to be pertinent here:

a) A reaction sequence, *e.g.*, of the type

$$\begin{aligned} &1)\ A_1 &&\rightarrow B_1 + X_1\\ &2)\ X_1 + A_2 &&\rightarrow B_2 + X_2\\ &\text{n-1})\ X_{n-2} + A_{n-1} &&\rightarrow B_{n-1} + X_{n-1}\\ &n)\ X_{n-1} + A_n &&\rightarrow B_n \end{aligned}$$

where A_i are reactants and B_i reaction (end-)products, and the intermediates X_2 are stable or even active particles (atoms, radicals), is not a chain reaction but an ordinary reaction sequence. In the terminology of *Christiansen* [2], in particular, it is called an open reaction sequence.

b) A reaction sequence of the type

$$\begin{aligned} &1)\ X_1 + A_1 &&\rightarrow B_1 + X_2\\ &2)\ X_2 + A_2 &&\rightarrow B_2 + X_3\\ &\text{n-1})\ X_{n-1} + A_{n-1} &&\rightarrow B_{n-1} + X_n\\ &n)\ X_n + A_n &&\rightarrow B_n + X_1 \end{aligned}$$

is a closed sequence according to *Christiansen* or a chain reaction in the sense of *Bodenstein* [the concept is due to *Bodenstein* (1913); the term "chain reaction" is due to *Christiansen* (1921)]. In a genuine chain reaction, the X_i are, in general, active particles. The decisive difference, however, is the appearance of particles of the kind X_1 during the last reaction step; this closes the sequence, which thus becomes a chain and which attains cyclic character. Every cyclic permutation of the chain is reasonable. It can easily be seen that the reaction sequence a) does not change into a closed sequence even if, for example, the first and the last steps are omitted.

c) The characteristic features of uranium fission and chemical reactions with chain branching do not follow simply from the chain nature of these reactions. The responsible step here is at least one act of chain branching. In normal chain reactions, the concentration of active particles (the "chain carriers") is given by the chain-initiating and chain- terminating reactions [not shown in scheme b)]; however, in reactions exhibiting chain branching, there are, in addition, special reaction steps that increase the number of chain carriers. In the case of the fission of uranium by neutrons (n) this may be written in simplified form as

$$U^{235} + n \rightarrow \text{decay products} + (1 + k)n$$

where $k > 0$; *i.e.*, a single neutron causes the fission of U^{235} into decay products, with simultaneous formation of more than one neutron (k need not be an integer if the reaction scheme is to represent some average behavior in the course of the various independent and parallel reaction steps). If the multiplication of active particles by chain branching is not compensated by a corresponding chain terminating reaction (*e.g.*, the capture of neutrons by cadmium in an atomic reactor), the number of chain carriers rises, the velocity of the reaction in turn increases with time (exponentially, at least at the beginning), and an explosion through chain branching occurs. In the case of chain branching, a reaction such as the following would have to be added to scheme b):

$$j)\ X_{j-1} + A_j \rightarrow B_j + 2\,X_j$$

[2] *I. A. Christiansen*, Z. physik. Chem., Abt. *B 28*, 303 (1935).

[*] The fact that there can be a desirable influence of solid walls, *e.g.*, in heterogeneous gas catalysis, shall not concern us in this paper.

known and frequently encountered rapid chemical reaction is the combustion of gas mixtures. If one considers a laminar flame burning at normal pressure on an appropriate burner, some idea of the rate of the chemical changes can be obtained by measuring the normal burning velocity Λ and estimating the depth δ of the reaction zone. Thus, Λ is the flow velocity of unburnt gas perpendicular to the flame front. The depth δ of the combustion zone amounts to 10^{-3} to 10^{-1} cm at atmospheric pressure. Frequently observed values are, *e.g.*, $\Lambda \approx 100$ cm/sec and $\delta \approx 0.01$–0.1 cm. This yields reaction times of about

$$t_R \approx \delta/\Lambda \approx 10^{-3}\text{–}10^{-4} \text{ sec}$$

Depending on the gas mixture used, the temperature in the chemical reaction zone rises from room temperature to final values lying between approximately 1500 and 3500 °K [**]. The unburnt gas enters the combustion zone and is first heated to 800–1000 °K by heat transport. Above this temperature, the continuously accelerating chemical reactions markedly influence the phenomena in the combustion zone. For a quantitative treatment, it is therefore necessary to collect data on the reaction mechanism and on the rates of the single reaction steps in the temperature range of 800 to *ca.* 3500 °K. (The pressure in the combustion zone remains constant to a good approximation.)

Experiments performed over the last fifty years seem to indicate that most combustion processes in gases are significantly influenced by chain and chain-branching reactions. Qualitatively, this automatically implies a definite reaction mechanism. Its characteristic feature is the appearance of chemically active species such as H, O, OH, or CH_3, which react rapidly (*i.e.*, with low activation energies) with the reactants and sometimes with intermediates, forming one new (ordinary chain step) or several new active particles (chain-branching steps) in the course of the reaction. The reaction sequence must be closed (cf. above [3,4]). Two well-known examples may be cited:

a) The essential steps in the hydrogen-bromine reaction are chain steps:

$$Br + H_2 \rightarrow HBr + H$$
$$H + Br_2 \rightarrow HBr + Br$$

b) In the reaction between hydrogen and oxygen:

$$(1)\quad H + O_2 \rightarrow OH + O$$
$$(2)\quad O + H_2 \rightarrow OH + H$$
$$(3)\quad OH + H_2 \rightarrow H_2O + H$$

reactions (1) and (2) are chain-branching steps and (3) is an ordinary chain step. Reactions of this type are exothermic or weakly endothermic. Their activation energies are generally less than 20 kcal/mole and frequently less than 10 kcal/mole, and a "steric factor" p [*] lying between 1 and 0.01 may be assumed. This means that, at high temperatures, with a gas kinetic collision number $Z \approx 3\times10^9$ collisions/sec (2000 °K, 1 atm), for instance, one particle participates in about $Z_r \approx Z \cdot p \cdot e^{-\frac{E}{RT}} \approx Z \cdot p \cdot 10^{-4}$ collisions per second, with sufficient relative energy and favorable mutual orientation of the colliding partners. For an active particle in this example, it can be expected that reaction will take place, on the average, after $Z/Z_r \leq 1/p\times10^4$ collisions. Its lifetime is then of the order of magnitude $1/Z_r \gtrsim 5\times10^{-7}$ sec. A comparable time resolution is in fact obtained in shock waves and detonations.

The formation of active particles by an initiating reaction plays a part in many processes in which diffusion and wall effects are of minor importance. Examples include initiation by sparks or shock waves, and detonations. The initiating reactions are generally strongly endothermic, *e.g.*:

	E_a (kcal/mole)	ΔH° (kcal/mole)
(1) $H_2 + M \rightarrow 2\,H + M$	103	103
(2) $Br_2 + M \rightarrow 2\,Br + M$	45,5	45,5
(3) $H_2 + O_2 \rightarrow 2\,OH$	50–70	20

E_a = activation energy; ΔH° = enthalpy of formation at 0 °K

Even at high temperatures, the rates of such reactions are usually smaller by several orders of magnitude than those previously mentioned. Even under the conditions prevailing in a hydrogen-oxygen detonation the first reaction is so slow that it can hardly be considered a chain-initiating reaction.

As far as combustion of this comparatively simple hydrogen-oxygen system is concerned, recent research has succeeded in satisfactorily accounting in a semiquantitative manner for even such extraordinarily short reaction times as $t_R \approx 10^{-6}$ sec by using reaction schemes of the type indicated above. However, in general, it must be confessed that at present we have only rather scant knowledge of the specific reaction mechanism and the rates of individual steps, especially for a large number of technically important hydrocarbon–air reactions.

Techniques for Investigating Fast Gas Reactions

To obtain kinetic data during short reaction times, special techniques, most of which have been developed in the last few years, must be employed. It is frequently impossible to predict the outcome of reactions at temperatures above 1000 °K from the results of experiments carried out under conditions in which these reactions proceed slowly, *viz.* at low pressure and temperature (cf., *e.g.*, investigations of explosion limits in

[**] Examples of extreme flame temperatures for various mixtures at atmospheric pressure:

$2\,H_2$–O_2: 3100 °K

C_2N_2–$2\,O_2$: 4900 °K

C_2H_2–$^3/_2\,O_2$: 3440 °K

[3] *W. Jost:* Explosions- und Verbrennungsvorgänge in Gasen. Springer, Berlin-Göttingen-Heidelberg 1939.

[4] *N. Semenov:* Chemical Kinetics and Chain Reactions. Clarendon Press, Oxford 1935; *C. N. Hinshelwood:* The Kinetics of Chemical Change. Clarendon Press, Oxford 1940.

[*] The factor p takes into account the fact that not every collision with sufficient relative energy leads to reaction. The mutual orientation of the colliding molecules, *etc.* must exert an influence (cf. Boltzmann's "sensitive" region [5]).

[5] *L. Boltzmann:* Vorlesungen über Gastheorie. J. A. Barth, Leipzig 1896, vol. 2.

closed vessels by *Lewis* and *Von Elbe* [6] and *Hinshelwood* [4], or "adiabatic compression" experiments by *Jost* and *Teichmann* [7]). It is never certain *a priori* whether a reaction mechanism assumed at low temperatures may not alter substantially when the temperature is raised; furthermore, because of the relatively large experimental error inherent in the determination of rate constants, extrapolations to higher temperatures, even with modest demands on accuracy, are no simple matter. What methods are at present available for investigating chemical reactions in the gas phase at 1000 °K? The technique of "rapid adiabatic compression" is advantageously applied at the lower limit of the temperature region (up to about 1000 °K). So far, its use has permitted measurement of induction times lying mainly in the millisecond range (cf. *Jost* et al. [8]). In conjunction with modern analytical techniques, the information to be gained with the help of this method is very promising.

Another approach is the investigation of flames at reduced pressures. If it is assumed that second-order reactions predominate, it follows that the reaction time t_R, and hence the width of the reaction zone, is approximately inversely proportional to the pressure: $t_R \sim \alpha\ 1/p$. Special techniques [*Egerton* and *Powell*] have permitted laminar flames to be produced at $\leq$ 10 mm pressure and with reaction zone widths of about 50 mm [9]. Local measurements with thermocouples and spectroscopic investigations are also possible and have already yielded valuable data, with promise of more. The accessible temperature region lies roughly between 1000 and 2500 °K. The experimental requirement is comparatively high; however, a great many exothermic reactions can be investigated in this manner.

In the present article, the discussion will be limited exclusively to the application of shock waves and detonations to problems in reaction kinetics. By using shock waves, any reasonably high temperature can be produced in a relatively simple manner. However, shock waves cannot be applied without due precautions to exothermic reactions, especially combustions, since the reaction itself might accelerate the shock wave. In comparison, endothermic processes, such as dissociation reactions, can be investigated easily. Detonations occur only in certain exothermic mixtures; however, their study has been refined to such a degree that they also offer a valuable tool for research in reaction kinetics.

In the following section, a brief description will be given of the properties of shock waves and detonations and of methods for generating these. Subsequently, a discussion will be given of the most important measuring techniques so far applied to kinetic investigations. Some typical results will be discussed.

[6] *B. Lewis* and *G. v. Elbe:* Combustion, Flames and Explosions of Gases. Academic Press, New York 1951.

[7] *W. Jost* and *H. Teichmann*, Naturwissenschaften *27*, 318 (1938); *Z.* Elektrochem., Ber. Bunsenges. physik. Chem. *47*, 262, 297 (1941).

[8] *A. Martinengo* and *H. Gg. Wagner*, Z. physik. Chem. N. F. *20*, 206 (1959); Forsch. Gebiete Ingenieurwes. *26*, 198 (1960).

[9] *Th. Grewer*, Ph.D. Thesis, Universität Göttingen 1959; *U. Bonne, Th. Grewer*, and *H. Gg. Wagner*, Z. physik. Chem. N. F. *26*, 93 (1960).

a) Generation and Properties

Figure 1 shows a simple apparatus for generating shock waves. A and C are two tubes of equal cross-section, which at the start of the experiment are separated by a

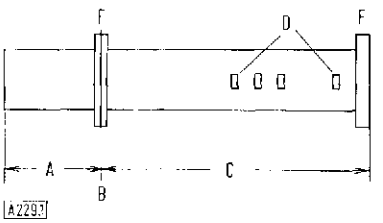

Fig. 1. Sketch of a setup for generating shock waves. A = Compression tube; B = diaphragm (plastic or metal foil); C = expansion or shock tube; D = observation windows; F = flanges. The pressure is higher in A than in C prior to rupture of diaphragm B.

membrane B (*e.g.*, cellophane or aluminum foil). The pressure in A (high-pressure or driving section) is higher than in C. If the membrane is caused to burst by increasing the pressure in A or by scratching the membrane, a flow process designated as a "shock wave" is produced in C after a brief transition region. It is expedient to use in A a driving gas of the smallest possible molar mass (*e.g.* He or H_2) [10]. Figure 2 shows the pressure relationships after the shock wave has been developed.

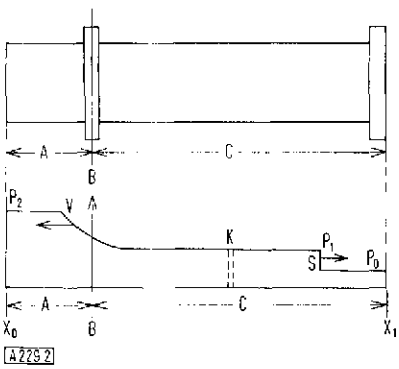

Fig. 2. Pressure relations shortly after formation of the shock wave S. P_0 = Initial pressure in C; P_2 = initial pressure in A; P_1 = pressure behind shock wave S; x_0 = end of tube A; x_1 = end of tube C; *S* moves in the direction of the arrow. *V* = Decay of pressure P_2 in A by a rarefaction wave. The arrow shows the direction of propagation. *K* = contact interface (boundary between the gases from A and C).

As shown in Figure 2, the shock wave S is characterized by an extremely steep pressure gradient; according to measurements on monatomic gases, the transition from P_0 to P_1 takes place within a very short time interval ($t \leq 10^{-9}$ sec). The pressure discontinuity propagates through C with a velocity greater than c_0, the velocity of sound in the gas at rest in C.

The shock wave compresses the gas in C; the work required for this comes from the (virtually isentropic) work of expansion of the gas in tube A. The pressure

[10] *E. F. Greene* and *J. P. Toennies:* Chemische Reaktionen in Stoßwellen. Steinkopff, Darmstadt 1959.

drop in A from P_2 to P_1 occurs in a rarefaction wave [*], the front V_0 of which moves into the gas A with the velocity of sound. With increasing pressure drop in the rarefaction wave (Figure 2, at the right of V_0), the temperature of the gas falls. Simultaneously, its kinetic energy increases. The gas in A is set in motion along the positive x-direction. Figure 3 is a distance *vs.* time diagram showing the traces corresponding to the events in A and C. Here the pressure drop in A is characterized by a "rarefaction fan". Along the straight lines V_0 to V_n in the x *vs.* t diagram, the temperature, the pressure, and the difference $(w-c)$ between the local velocity w of the gas particles and the local velocity of sound c are constant [**]. A complete description of the phenomena up to the point of equilibration of the pressure in a shock tube is fairly complicated (cf. for example, *Oswatitsch* [11]).

Here we are only interested in the first phase, lasting approximately until the rarefaction wave V has reached the end of tube A.

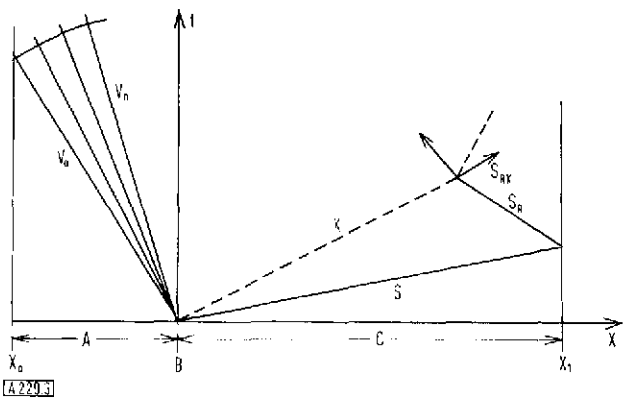

Fig. 3. Distance *vs.* time diagram of traces of the various phases of flow in tubes A and C during the first stage of pressure equalization. V = rarefaction fan, which characterizes the drop of the initial pressure P_2 in A; S = incident shock wave in positive x-direction; S_R = shock wave reflected from the closed end x_1 of tube; K = contact interface of the gases from A and C; S_{RK} = possible interaction of S_R and contact interface (see text).

Therefore, disturbances which spread out in the positive x-direction as soon as V_0 has reached the end x_0 need not be considered. If the shock tube is not too long, it can be assumed that S propagates during this phase with constant velocity. As soon as the shock wave S reaches the end of the tube, x_1, a further property of shock waves is observed. Rigid walls reflect shock waves in the form of shock waves. The shock wave S_R, which in this case is reflected perpendicularly, moves into an already compressed gas and thereby causes further compression and heating. In addition, the trace K appears in Figure 3. This represents the propagation of the "contact interface" that separates the gas heated by compression in the shock wave from the gas cooled by expansion in A. The density changes on passing from onee of sid K to the other; the pressure remains constant. After a certain time interval, the reflected shock wave S_R reaches the contact interface (Figure 3). Various phenomena can occur at that moment, depending on the variables of state of the gases in front of and behind K. Depending on the locus of interaction, either a shock wave or a rarefaction wave can be set in motion along the positive x-direction. If special conditions are maintained, however, these can prevent disturbances from spreading in the positive x-direction. This latter case is of a certain importance with regard to the construction of special shock tubes, which will be discussed more fully later.

Theoretical treatment of phenomena occurring in a shock tube, as described qualitatively above, is comparatively simple [11–13]. The changes in the variables of state caused by a shock wave in a chemically inert gas can be described by the laws of conservation of mass, momentum, and energy, and by the equation of state of the gas. Experiments show only a slight dependence of the shock wave on wall effects. Consequently, a "one-dimensional" approximation of the flow often yields excellent agreement between theory and experiment. (Generally, the shock front forms an only very slightly bent surface, practically perpendicular to the tube wall.) The state of the gas immediately behind the shock front may be expressed as a function of a single parameter, either the velocity of the shock wave or the ratio $S/c_0 = M$, its Mach number, if the simplifying assumption is made that the specific heat of the gas is constant and that the effects of friction and heat transfer are negligible.

Theory then yields for the pressure ratio:

$$\frac{P_1}{P_0} = \frac{2\varkappa M^2 - (\varkappa-1)}{\varkappa+1}$$

where $\varkappa$ = ratio of the specific heats C_p/C_v. For large Mach numbers,

$$P_1/P_0 \sim M^2$$

Mach numbers and pressure ratios P_1/P_0 for two gases are shown in Table 1.

Table 1. Mach numbers and P_1/P_0 for Ar ($\varkappa = 1.67$) and air ($\varkappa = 1.40$)

M	P_1/P_0 ($\varkappa \approx 1.67$)	P_1/P_0 ($\varkappa \approx 1.40$)
1	1	1
1,5	2.57	2.5
2	4.75	4.5
3	11.10	10.0
4	19.75	18.5
5	31.0	29.0

The temperature ratio T_1/T_0, which is of particular interest, depends in a somewhat complicated manner on M:

$$\frac{T_1}{T_0} = \frac{2\varkappa M^2 - (\varkappa-1)}{\varkappa+1} \cdot \frac{(\varkappa-1)M^2 + 2}{(\varkappa+1)\cdot M^2}$$

Mach numbers and temperature ratios T_1/T_0 are shown in Table 2.

It should be pointed out that at equal values for P_1/P_0 the temperature ratio T_1/T_0 is always larger during compression

[*] Rarefaction shock waves, *i.e.*, sudden drops in pressure, cannot occur, owing to the laws of thermodynamics.

[**] This is valid for a tube of constant cross-section and during the first phase of pressure decay, as long as V_0 has not yet reached x_0.

[11] *K. Oswatitsch:* Gasdynamik. Springer, Vienna 1952.

[12] *R. Sauer:* Einführung in die theoretische Gasdynamik. Springer, Berlin-Göttingen-Heidelberg 1960.

[13] *R. Courant* and *K. O. Friedrichs:* Supersonic Flow and Shock Waves. Interscience Publishers, New York 1948.

Table 2. Mach numbers and values of T_1/T_0

M	T_1/T_0 $\varkappa \approx 1.67$	T_1/T_0 $(\varkappa \approx 1.40)$
1	1	1
1,5	1.49	1.34
2	2.09	1.70
3	3.65	2.60
4	5.90	4.1
5	8.7	5.80

by a shock wave than during an adiabatic-isentropic compression. This results from the increase of entropy of the gas behind the shock front. Compression by a shock wave is an irreversible process (cf. Fig. 4).

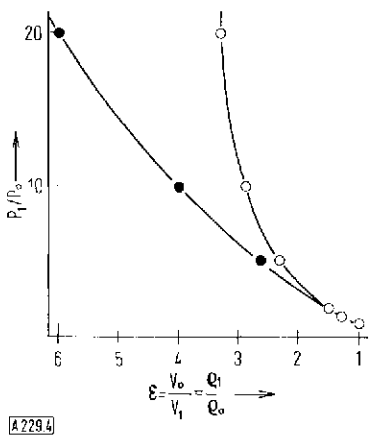

Fig. 4. Corresponding pressure and temperature relationships for isentropic (curve —●—●—) and shock wave compression (curve —o—o—) of a noble gas with $\varkappa = C_p/C_v = 1.67$ as a function of the density ratio ϱ_1/ϱ_0 before and after compression. In this case, ϱ_1/ϱ_0 is equal to the compression ratio $\varepsilon = V_0/V_1$ (where V is the volume which the gas assumes upon compression by a piston in an otherwise closed vessel).

In conclusion, as an example, some values are given for the incident and reflected shock waves in a shock tube employing H_2 as driving gas and Xe in the test section.

Starting condition:

H_2: $T_0 = 300\,°K$; $P_0 = 10$ atm

Xe: $T_0 = 300\,°K$; $P_0 = 1$ cm Hg

1. Incident shock wave:

$M_1 = 4$; $P_1 = 19{,}8$ cm Hg; $T_1 = 1764\,°K$; $S_1 = 712$ m/sec

2. Reflected shock wave:

$P_R = 99{,}3$ cm Hg; $T_R = 3750\,°K$; $S_R = 379$ m/sec

The brief introduction to the physics of shock waves given above is sufficient for present purposes. The question of the advantages and limitations that are to be expected from an application of shock waves to problems in reaction kinetics will now be discussed.

b) Advantages and Disadvantages of the Application of Shock Waves

The decisive advantage in applying shock waves is the extremely brief time, about 10^{-9} to 10^{-10} sec, during which the gas mixture is heated uniformly over almost the complete cross-section of the tube. In this interval, a given molecule experiences only a few collisions (< 10), and, as experiments show, this is insufficient to effect a substantial chemical conversion. Therefore, the initiation of a chemical reaction can be investigated under well-defined conditions [*].

If, for reasons to be discussed later, the investigations are restricted to comparatively fast reactions ($t_R \leq 5$ msec) and if the tube diameter is sufficiently large, it can then be assumed, with a high degree of probability, that all wall effects, *e.g.*, radical recombination, may be neglected. An estimate of the wall effects is easy to make: The time required for a particle (*e.g.*, a hydrogen atom) to diffuse from the center of the tube to the wall controls recombination of active particles at the wall. With a tube diameter of $2r = 2$ cm, this time t_D is of the order of magnitude of 10^{-1} to 10^{-2} sec (for $T = 1500\,°K$ and $P = 1$ atm).

$$t_D \approx \frac{r^2}{2D_H} \approx \frac{1}{2 \cdot 20} \text{ sec} \approx 25 \text{ msec}; \quad D_H \approx 20\,\text{cm}^2/\text{sec}$$

Compared with the usual reaction times of less than 1 msec, t_D is long. In any case, the diameter of the tube can always be made large enough to keep surface effects negligible. Formation of radicals at the wall of the tube does not take place, since the wall surface remains essentially at room temperature during the period of measurement.

If measurements are carried out behind the reflected shock wave, a different type of wall influence usually has to be considered, *viz.* effects arising from interaction between the reflected shock wave and the boundary layer, established shortly before by the gas flow behind the incident shock wave. In certain circumstances, relatively large inhomogeneities may exist in the variables of state of gases in tubes of small diameter when measured in a plane perpendicular to the tube axis. Experiments on monoatomic gases performed by *Cohen* and *Strehlow* [14] and *Skinner* [15] show that these effects are only small; however, these disturbances increased in shock tube experiments with, for example, gaseous hydrocarbons. Apart from this source of error, which must sometimes be taken into account, shock wave experiments are an excellent means for isolating reactions in the gas phase from other effects and for studying them under uniform conditions.

Another advantage lies in the relatively low experimental requirements needed for the generation of comparatively high temperatures (for chemical purposes, up to about 6000 °K). The pressure region to be investigated can be varied within fairly wide limits by an appropriate choice of the initial pressures in tubes A and C. (The ratio of temperatures T_1/T_0 depends solely upon the ratio of the pressure P_2 in A to the pressure P_0.)

What disadvantages are to be contended with? The basic limitation on the application of shock waves is the comparatively short time available for measurements – the brief interval during which perturbations

[*] Occasionally, one has to consider the time that elapses until equilibrium of the internal degrees of freedom is obtained. In general, these processes take place rapidly in comparison with chemical reactions. In the case of a diatomic molecule, *e.g.*, Cl_2, the time t necessary to reach equilibrium among the vibrational degrees of freedom is of the order of magnitude of microseconds ($T \approx 1500\,°K$, $P = 1$ atm). The corresponding time for equilibration of the rotational degrees of freedom is of the order of magnitude of 10^{-8} sec (cf. page 204).

[14] *R. A. Strehlow* and *A. Cohen*, J. chem. Physics *30*, 257 (1959).

[15] *G. B. Skinner*, J. chem. Physics *31*, 268 (1959).

caused by flow processes in the shock tube are without influence. Principally, there are two causes for this. As soon as the rarefaction wave V_0 reaches the end of tube A, it reverses its direction and then follows behind the shock front. After some time, this effects an attenuation of the shock front; *i.e.*, the values of the variables of state behind the shock front then depend upon time. The onset of this disturbance can be postponed by using a long high-pressure tube. Furthermore, for incident shock waves, the time available for measurements is limited to the time of passage past the place of measurement of either the contact interface K or the reflected shock wave S_R from tube end x_1. If it is desired to carry out measurements behind the reflected shock wave only, the measurement time is usually restricted by the disturbance which evolves from interaction of the reflected shock wave and the contact interface (Figure 3).

In Table 3 a list is given of the times available for measurements as determined by the times of passage of shock wave and contact interface for incident shock waves of various Mach numbers. The place of measurement is at a distance of 2 m from the membrane.

Table 3. Measurement times at distance of 2 m from the membrane (gas in the experimental tube is Ar)

M	t [msec]	T_1 [°K]
1.205	16.8	355
1.408	7.44	420
1.598	4.61	480
1.939	2.61	610
2.236	1.85	715
3.070	0.993	1075
4.502	0.554	2100
7.182	0.310	5050

Similar relationships hold for measurement times behind reflected shock waves. Hence, unless very long shock tubes are used (which lead to difficulties owing to the effect of the increasing boundary layer behind he shock front) only chemical reactions with reaction times of milliseconds or less are suitable for shock-wave studies.

Because of the short times available for measurements without disturbances, it has so far been impossible to extract samples of the gas mixture from behind the shock front [*]. The course of the chemical reactions must be followed by physical methods [**]. The available techniques will be described in the next section.

c) Techniques for Measuring the Velocities of Shock Waves

A prerequisite for the evaluation of data on any given quantity connected with the course of a chemical reaction is a knowledge of certain basic values of the variables involved. The variables of interest in shock-wave experiments are, *e.g.*, pressure, temperature, and density immediately behind the shock front, where chemical reaction is still insignificant. Direct simultaneous measurement of two variables would be advantageous; however, attempts to determine the density by means of the Mach–Zehnder interferometer have proven satisfactory in only a few cases. In most instances, one must rely on an indirect method. As long as no significant chemical reaction has taken place, the variables of state are dependent upon the velocity of the shock wave and the values for the variables of state of the gas that has not yet been affected by the shock wave. Measurements of the shock-wave velocity can be made easily and with sufficient accuracy. It is expedient to carry out the determinations in the immediate vicinity of the location, where the changes in the variables associated with the chemical reaction are to be observed. In this way, it is possible to make corrections for the influence of the minor, but not always negligible, deceleration of the shock wave caused by the generation of the boundary layer. The temperature ratio to be calculated depends approximately on the square of the Mach number. It follows that uncertainties in the velocity measurement exert a relatively large influence.

The velocity of the shock wave is calculated from the distance between two or more measurement points and the time intervals between the signals produced by the passing shock wave. The most common method for obtaining a signal from the shock wave depends on the deflection of a narrow, nearly parallel light beam by the density gradient of the shock front. Figure 5 shows a typical arrangement. This arrangement is inexpensive, can be assembled quickly, and is very reliable. The time resolution is of the order of microseconds, and with a carefully constructed arrangement, its limitations as to accuracy are mainly due to the slight curvature of the shock front. The method fails if the change of density is less than 1 % of the density of air under standard conditions of temperature and pressure. A number of variations of this principle are given in the literature, but these will not be discussed here. A compilation is given, *e.g.*, by *Toennies* and *Greene* [10].

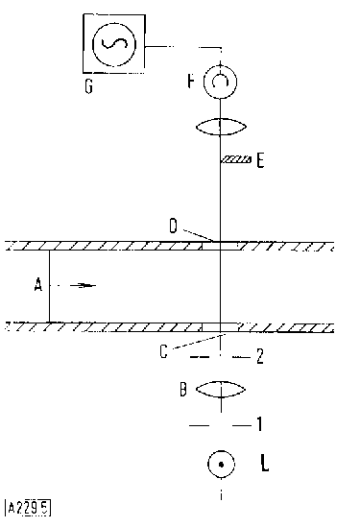

Fig. 5. Sketch of setup in which the shock wave (A) induces a signal by deflection of a narrow beam of light. The slit 1 is projected on the plane of the aperture (E) by the lens (B). The image is made by the narrow light beam which is passed by the slit 2 and which falls, after passing through windows C and D, exactly normal to the axis of the shock tube. The aperture E is adjusted in such a way that it just completely covers the image of slit 1. As soon as the shock wave crosses the light beam, the light is deflected to the side of the aperture by the density gradient in the shock front and impinges on the photocathode (F) of a photomultiplier [*]. The electric signal is transmitted, with the help of a cathode amplifier, into an oscilloscope (G).

[*] The application of fast-recording "time-of-flight" mass spectrometers (10^{-4} sec per spectrum) is an analytical possibility.

[**] A method that approximately "freezes" the state of the gas mixture behind the shock front by means of rapid cooling has recently been described by *Glick*, *Squire*, and *Hertzberg* (cf. page 201).

[*] Such instruments use secondary electron emission to achieve signal amplification.

A basically different method utilizes measurement of the change of resistance of very thin metal foils (of about a few microns thickness), the temperature of which is changed by the hot gas behind the shock front. The response time is also in the microsecond range and reliable measurements can be performed above Mach numbers of 3.

Determination of the velocity of shock waves pressure changes is not recommended, since the piezoelectric transducers so far available are sufficiently sensitive only to strong shock waves. Furthermore, the transducer is quite susceptible to interference created within it by the motion of induced shock waves.

Occasionally, the heated gas behind the shock front is used to fire ionization electrodes, which have been precharged to just below their discharge level, as soon as the shock wave passes the electrodes. This method is simple and well suited for strong shock waves ($M > 4$). Again, a time resolution of 10^{-6} sec can be attained here.

d) Methods for Measuring Quantities Connected with a Chemical Reaction

Since it is nearly always the time dependence of the variables behind the shock front that is measured, a few remarks should first be made concerning the measurement of time. In principle, determination of the time interval Δt between two values of a quantity behind the shock front must make allowances for the motion of the gas at the point of measurement; for an illustration of this see Figure 6, where traces of the shock front S and the motion of particles behind the shock front are shown.

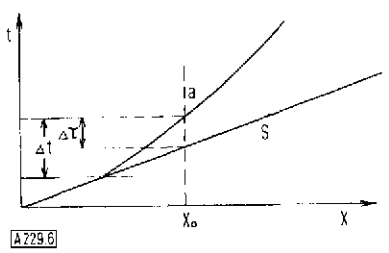

Fig. 6. A time *vs.* distance diagram showing the paths of an incident shock wave S and of the gas particles set in motion behind the shock front. The point of measurement is at x_0.

An observer at x_0 measures the time difference $\Delta\tau$ between passage of the shock front and arrival of the volume element *a*. Actually, however, the volume element *a* has already been subjected to the influence of the shock wave for a time Δt. This time interval is of real importance for measurement of reaction kinetics. For a constant flow velocity w behind the shock front we have:

$$\Delta t = \Delta\tau \cdot \frac{S}{S-w}$$

where

S = velocity of the shock wave

w = flow velocity behind shock wave measured relative to the wall of the shock tube (observer at rest).

Applying the law of conservation of mass:

$$S \cdot \rho_0 = (S-w)\,\rho_S$$

where

ρ_0 = initial density

ρ_S = density just behind shock front

we find

$$\Delta t = \Delta\tau \cdot \rho_S/\rho_0.$$

In general, therefore, the variation of density must be known in order to evaluate a variable behind the shock front. This difficulty vanishes only in the case of measurements carried out in gas mixtures behind the shock wave S_R, *i.e.* the shock wave reflected at the end of the tube, since there the velocity of the flowing gas particles w is zero relative to the tube wall; hence Δt equals $\Delta\tau$.

d 1) Measurement of the Variation of Density; Dissociation of O_2; Interferometric Methods

Measurement of the variation with time of a variable of state or some other variable directly related to that parameter (such as the index of refraction) generally permits conclusions to be drawn only about the over-all reaction. For example, data on the total time of reaction or – in experiments to be described later – data on the induction period of the reaction are obtained. Detailed conclusions can be drawn about the value of rate constants of the individual reaction steps only when dealing with a very simple reaction with a uniquely known reaction mechanism. Examples are dissociation reactions according to the scheme

$$M + Br_2 \rightarrow 2\,Br + M$$

or

$$M + O_2 \rightarrow 2\,O + M\,[*]$$

Measurements can be made in these cases (*e.g.*, with the help of a Mach-Zehnder interferometer) of the change of the index of refraction behind the shock wave. The variation of the density can be calculated from the data obtained if it can be assumed that the mean molar polarization is constant, or constant to a good approximation[**]. At a non-absorbed wavelength, the relationship between index of refraction and density of gases is (cf., *e.g.*, *Born* [16]):

$$(1)\quad n-1 \approx \frac{\rho}{m} \cdot 2\pi \cdot \sum_i x_i \alpha_i$$

where

α_i = molar polarization (cm^3/mole)
x_i = mole fraction
n = index of refraction
m = mean molecular weight
ρ = density

On the other hand, the variation of density with time can be calculated at a known velocity of the shock wave from the conservation laws, the equation of state of the gas, and relationships for the rate of formation of the various particles.

A trial-and-error calculation procedure is repeated for various assumed rates of formation until agreement with experimental data is reached. This method is very

[*] Available experimental data indicate that this process involves a purely bimolecular reaction between the starting materials. Chain reaction mechanisms apparently do not occur.

[**] In some cases, the molar polarization is found constant in spite of the reaction.

[16] *M. Born:* Optik. Springer, Berlin-Göttingen-Heidelberg 1933.

cumbersome and the calculation difficult to perform without a computer, unless the measurements are restricted to the initial stages of the reaction, or the gas to be investigated is diluted with large amounts of an inert gas (Ar, N_2) [**].

So far, only one chemical reaction has been studied in this way. *Byron* [17] and *Mathews* [18] measured the rate of dissociation of O_2 in the temperature region 3000 to 4900 °K. The precision of their experiments appears to be quite good; the authors give the rate constant to an accuracy of within a factor of two to three. Thus, k_{O_2} may be expressed in this temperature region by the relation

$$k_{O_2} \approx 5 \cdot 10^6 \cdot T^{1/2} \left(\frac{59380}{T}\right)^3 \exp\left(-\frac{118760}{R \cdot T}\right) \text{ liters/mole/sec}$$

where 118, 760 cal/mole corresponds to the dissociation energy of oxygen. The term $(59380/T)^3$ is included to account for the participation of the vibrational energy of the molecules in dissociation.

More often, the Mach-Zehnder interferometer has been used to carry out measurements of relaxation times of vibrations of di- and polyatomic molecules.

d 2) Density Measurement by Absorption of Soft X-Rays by Added Xenon

Determination of the variation of density by means of absorption of soft X-rays ($\lambda \approx 5$–20 Å) by admixture of heavy rare gases such as xenon was first applied to detonations in hydrogen-oxygen gas mixtures by *Kistiakowsky* and *Kydd* [19] (cf. page 209). Later, this method was used for reactions behind shock waves by *Kistiakowsky* and *Gardiner* [20] and by *Pink*, *Knight*, and *Duff* [21].

This method allows the time to be resolved to within 10^{-6} sec. Its main difficulty lies in obtaining a source of soft X-rays that is sufficiently intense and constant over periods of about 100 to 500 microseconds. Furthermore, the kinetics of the reactions to be studied may be influenced by large additions of rare gas (40–95 %). *Pink*, *Knight*, and *Duff* measured the rate of dissociation of oxygen in a shock tube between 3000 and 6000 °K. Experiments of a different kind by *Camac* and *Vaugham* (cf. page 198), which were carried out with very high time resolution ($t \approx 5\times10^{-7}$ to 1×10^{-6} sec), make it seem likely that, in this temperature region, rotational and vibrational equilibria in the oxygen molecule are reached faster than the dissociation equilibrium by a factor of 10 to 1000. Therefore, the temperature behind the shock wave prior to dissociation can be determined with sufficient accuracy.

Results of measurements by various authors are compiled in Table 4, which also includes the constant of recombination k_R for oxygen atoms, which is related to the dissociation constant k_D of O_2 by the equation

$$k_R = \frac{k_D}{K_c}$$

where K_c is the equilibrium constant at the temperature of measurement and equals $\frac{[O]^2}{[O_2]}$

Table 4. Recombination rates of oxygen atoms

[°K]	Authors	Method	Third collision partners	k_R [liters²/mole²/sec]
3500	*Pink, Knight, Duff*	X-rays	O_2 Xe O	$4.6\cdot10^8$ $1.3\cdot10^8$ $1.4\cdot10^9$
3500	*Byron*	*Mach-Zehnder*	O_2 Ar O	$4.8\cdot10^8$ $4.5\cdot10^7$ $9.9\cdot10^8$
3500	*Matthews*	*Mach-Zehnder*	O_2	$8\cdot10^8$
3500	*Camac, Vaugham*	Ultraviolet absorption	O_2 Ar O	$1.6\cdot10^8$ $5.2\cdot10^7$ $1.3\cdot10^9$
3500	*Evans, Schexnayder*	Ultraviolet absorption	O_2	$1\cdot10^9$

The last two entries in the table show measurements based on the light absorption of oxygen molecules in the region of the Schumann-Runge continuum near 1450 Å. This method is described further below.

Kistiakowsky and *Gardiner* used the absorption of soft X-rays to measure the rate of dissociation of hydrogen in the temperature region 3000–4500 °K. They worked with mixtures of 17 % H_2 in Xe and 47 % H_2 in Xe.

Their results are shown along with older measurements by *Farkas* and *Sachsse* [22] in Table 5. For collision partners Xe and Ar, on the basis of well-known, simple assumptions, one obtains:

$$k_D = A \cdot T^{-1/2} \exp\left(-\frac{D}{R \cdot T}\right) \text{ liters/mole/sec}$$

and for H_2

$$k_D = A \cdot T^{-3/2} \exp\left(-\frac{D}{R \cdot T}\right) \text{ liters/mole/sec}$$

Table 5. Rate of dissociation of H_2

T [°K]	Authors	Method	Collision partner	A [liters/mole/sec]
300	*Farkas, Sachsse*	photochem. dissociation	H_2 Ar H	1.8×10^{17} 2×10^{14} 2×10^{14}
3000 to 4500	*Kistiakowsky, Gardiner*	shock tube	H_2 Xe H	1.8×10^{17} 1.8×10^{14} 1.2×10^{15}

where D is the dissociation energy of hydrogen at absolute zero: $D = 4.477$ ev $= 103.23$ kcal/mole.

Kistiakowsky and *Gardiner* estimate their measurements of k_D to be accurate to within a factor of 2 to 4. Within the temperature range 300 to 4500 °K, k_D changes by about 25 orders of magnitude; it is still remarkable that, with the

[**] In the case of extreme dilution, the system of equations can be simplified to such an extent that analytical expressions can be derived.

[17] *S. R. Byron*, J. chem. Physics *30*, 1380 (1959).

[18] *D. L. Mathews*, Phys. Fluids *2*, 170 (1959).

[19] *G. B. Kistiakowsky* and *P. H. Kydd*, J. chem. Physics *25*, 824 (1956).

[20] *G. B. Kistiakowsky* and *W. C. Gardiner*, J. chem. Physics *35*, 1765 (1961).

[21] *J. P. Pink*, *H. T. Knight*, and *R. E. Duff*, J. chem. Physics *34*, 1942 (1961).

[22] *L. Farkas* and *H. Sachsse*, Z. physik. Chem. Abt. B *27*, 111 (1934).

relatively primitive assumptions of the kinetic theory of gases, a sufficiently accurate reproduction of the experimental results is nevertheless obtained.

d 3) Spectroscopic Methods

A further method for studying reaction kinetics in shock waves is available if light-absorption can be used to determine the time-dependent change of concentration of one or more suitable species. This demands that the experimental setup should have a sufficiently high time-resolution. Continuous, band, and line spectra can be used. Knowledge of the dependence of the extinction coefficient on temperature and concentration is very essential here. At the present time, this is known for only a few molecules and a number of atoms; light-absorption measurements on atoms are generally excluded, since their line spectra mostly lie in the vacuum ultraviolet (Schumann region), and their measurement frequently entails excessive experimental difficulties. This is true, for example, in the case of the otherwise quite suitable method for determining the concentration of free hydrogen atoms by absorption in the Lyman series.

First, as an example of an endothermic reaction, the measurements of the rate of dissociation of Br_2 performed by *Palmer* and *Hornig* [23], using the light absorption of Br_2 in the region around 4390 Å will be discussed. The experimental apparatus is shown schematically in Figure 7.

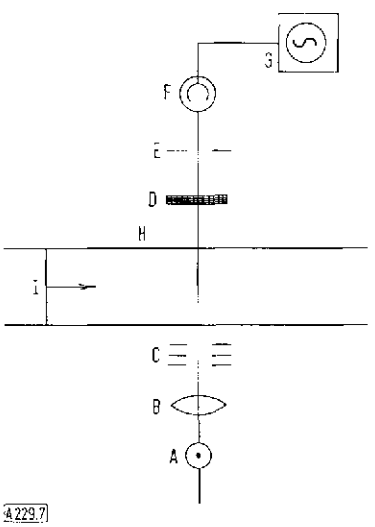

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Fig. 7. Schematic diagram of an apparatus for measuring absorption of light by bromine molecules behind the incident shock wave (I). The lens (B) forms an approximately parallel beam of light, from which the three slits (C) separate a narrow beam approximately 1 mm in width. The interference filter (D) has a half-width of 180 Å and permits only light close to 4390 Å to reach the photocell (F) (RCA 931 A). Slit (E) limits the solid angle of the light emission of the bromine molecules. Light emission starts as soon as the molecules are heated up by the shock wave (I). The signals are recorded on an oscilloscope (G).
A: light source, H: glass tube

Bromine has continuous absorption in the region from the ultraviolet to approximately 5100 Å. This is followed by a band system at longer wavelengths. A filter separates out a wavelength interval in the neighborhood of 4390 Å. In Fig. 8 oscillograms obtained from shock waves in two different mixtures are reproduced.

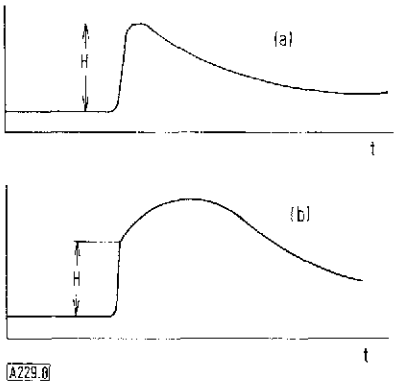

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Fig. 8. Two oscillograms obtained with the experimental arrangement of *Palmer* and *Hornig*. The variation with time of the absorption of the Br_2 molecules upon passage of a shock wave through the light beam (cf. Fig. 7) is shown qualitatively. First a sudden rise in the absorption due to compression from the shock wave is observed. The subsequent change must be ascribed to dissociation of the bromine. a) 10 % Br_2 in Ar; b) 100 % Br_2. Ordinate: % absorption; abscissa: time

The decrease in temperature due to dissociation of Br_2 behind the shock front is comparatively small in the 10% bromine in argon mixture. Pure Br_2 behaves quite differently. Here the decrease of temperature is so great that, despite the onset of dissociation, the concentration (particles per cm^3) of Br_2 increases. As a consequence, an increase in the absorption behind the shock front is observed.

The extinction coefficient of Br_2 can be determined from the height H of the deflection of the oscilloscope beam immediately after passage of the shock front. It can be assumed that at this point there is still no substantial dissociation of Br_2 and that all degrees of freedom of the molecule are in equilibrium; *i.e.*, rotation and vibration have been activated. According to measurements of *Hornig* [24, 25], *Greenspan* [26], and others, excitation of rotation in a diatomic molecule requires about five to ten collisions. It is known from sonic dispersion measurements (cf. [27]) that excitation of vibration requires approximately 10^2 to 10^3 collisions, while about 10^5 collisions are needed for dissociation at the experimental temperature (cf. below). Hence, there is a sufficiently large interval in which the above assumption is satisfied. With due regard to these relations, the temperature was obtained from a measurement of the velocity of the shock wave, and the concentration of Br_2 prior to the onset of the reaction was determined from the initial concentration of Br_2 in front of the shock wave. From measurements at varying shock-wave velocities the dependence of the extinction coefficient on temperature and concentration of Br_2 can be determined.

[23] *H. B. Palmer* and *D. F. Hornig*, J. chem. Physics *26*, 98 (1957).

[24] *D. F. Hornig* and *E. F. Greene*, J. chem. Physics *21*, 617 (1953).

[25] *W. H. Andersen* and *D. F. Hornig*, Molecular Physics *2*, 49 (1959).

[26] *M. Greenspan*, J. acoust. Soc. America *22*, 568 (1950).

[27] *K. F. Herzfeld* and *T. A. Litovitz*: Dispersion and Absorption of Ultrasonic Waves. Academic Press, New York 1958.

Palmer and *Hornig* evaluated only the initial stages of the rise of the oscilloscope trace behind the shock front. This simplifies the method of evaluation considerably. A detailed discussion of this topic cannot be given here; however, a summary of the various corrections which had to be applied in spite of the simplifying assumptions should be mentioned.

Allowances were made for the following:

1) The influence of the decreasing temperature behind the shock front on the extinction coefficient and the overall density.

2) The influence of the motion of the gas behind the shock front: conversion of "laboratory" time $\Delta\tau$ into "real" time Δt (cf. page 195).

3) The influence of light emission of the gas upon absorption.

The influence of the density gradient behind the shock front on the deflection of the light beam traversing the shock tube (Fig. 7) was not considered. Since slit (2) is kept very narrow (about 1 mm), deflection of the light beam at the edges of the slit may simulate an additional absorption. The effect is probably small in 10 % bromine in argon mixtures; however, in experiments with pure Br_2, it might be appreciable.

The measurements were carried out in the temperature region between 1300 and 2200 °K and yielded values for the rate constants of the reactions

$$Br_2 + Ar \xrightarrow{k_1} 2\,Br + Ar$$

and

$$Br_2 + Br_2 \longrightarrow 2\,Br + Br_2,$$

that are in good agreement with those determined at lower temperatures. Here again it is remarkable that the value of the constant k_1 is known in the region 300 to 2200 °K since it varies within this region by 27 powers of ten. A good approximation of its temperature dependence is given by the expression

$$k_1 \approx 2 \cdot 10^7\, T^{1/2} \left(\frac{45\,500}{R\cdot T}\right)^3 \cdot \exp\left(-\frac{45\,500}{R\cdot T}\right) \text{liters/mole/sec}$$

(where T lies between 1000 and 2200 °K).

The term $(45,500/RT)^3$ is meant to take into account the contribution of the vibrational degrees of freedom to the reaction at higher temperatures. The energy of dissociation of Br_2 amounts to 45.5 kcal/mole.

It is very probable that a three-body collision mechanism governs the reverse reaction, *i.e.* recombination of Br atoms to Br_2 molecules [3,4].

$$Br + Br + M \rightarrow Br_2 + M\,[*]$$

M is a third collision partner; it can be a Br_2 molecule or any added inert gas. During recombination, M takes up at least part of the liberated energy so that the nascent Br_2 molecule remains stable. In certain circumstances, a mechanism of recombination such as

(a) $Br + M \rightarrow BrM$

(b) $BrM + Br \rightarrow Br_2 + M$

must also be considered. BrM is a labile intermediate between Br and an appropriate partner. Mechanisms of this kind were first suggested by *Eyring* [28] to explain his measurements of the recombination of iodine atoms. The reaction rate constant k_2 can be computed from measurement of the rate constant k_1 for the dissociation of Br_2 and from the equilibrium constant K_c, which is known from thermodynamic data. From the known relationship

$$K_c = \frac{[Br]^2}{[Br_2]} = \frac{k_1}{k_2},$$

it follows that

$$k_2 = \frac{k_1}{K_c}$$

Palmer and *Hornig* give the values $k_2 = 5.3\times10^8$ liters^2/mole^2/sec at $T = 1380$ °K and $k_2 = 2.9\times10^8$ liters^2/mole^2/sec at $T = 1700$ °K with Ar as the third collision partner. Only a slight dependence on temperature of the recombination rate constant k_2 is observed. The energy of activation E_2 of the reaction $Br + Br + M \rightarrow Br_2 + M$ must be equal to the difference between the activation energy E_1 of the forward reaction $Br_2 + M \rightarrow 2\,Br + M$ and the dissociation energy D. However, in the present case, $E_1 \approx D$, and therefore $E_2 \approx 0$.

It can be derived from these data that a small decrease of the rate constant k_2 with increasing temperature occurs, but whether this effect is real or not cannot be decided with certainty at present, because the accuracy of the method of measurement is not yet sufficient. In any case, experiments on Br_2 by *Britton* and *Davidson* [29], who used an experimental arrangement quite similar to that described above, showed, to all practical purposes, no temperature dependence for k_2. Experiments of a similar kind on I_2 performed by *Britton, Davidson, Schott,* and *Gehmann* [30] indicated a decrease in the rate constants for recombination of I_2 with increasing temperature. Some of the results of investigation using shock waves on Br_2 and I_2 are summarized in Table 6.

Table 6. Rates of recombination of Br or I atoms (Ar as third collision body). All values in liters^2/mole^2/sec

T [°K]	1380	1538	1770	Authors
k_2 (Br)	5.3×10^8	3.8×10^8	2.9×10^8	*Hornig* and *Palmer*
	3.5×10^8	3.3×10^8	3.1×10^8	*Davidson* and *Britton*
k_2 (I)	4.1×10^8	3.6×10^8	3.0×10^8	*Davidson* et al.

Reference has already been made on page 196 to a similar optical method for the measurement of the dissociation of oxygen at high temperatures (3000–9000 °K). *Camac* and *Vaughan* [31] and *Evans* and *Schexnayder* [32] utilized the change in light absorption of oxygen molecules behind the shock front for measuring their rate of dissociation. The conntiuous absorption of the oxygen molecule in the region near 1470 Å was used. The difficulty with this method resides mainly in the determination of the extinction coefficient for oxygen as a function of temperature and concentration. Furthermore, consideration must be afforded to the influence of vibrational relaxation on the calculated temperature behind the shock front prior to the onset of the reaction. *Camac* and *Vaughan* [31] carried out special measurements with a high time-resolution, showing that this effect can be neglected below 6000 °K. The same authors give the following expression for the dissociation rate constant in a mixture of 98 % Ar and 2 % O_2 in the temperature region 3500 to 7000 °K:

$$k_{D(Ar)} \approx 6\cdot10^{10} \left(\frac{118\,800}{R\cdot T}\right) \cdot \exp\left(-\frac{118\,800}{R\cdot T}\right) \text{liters/mole/sec}$$

[*] The same holds for a number of other simple reactions, such as $H + H + M \rightarrow H_2 + M$ or $I + I + M \rightarrow I_2 + M$.

[28] *H. Eyring* and *G. V. Rollefson*, J. Amer. chem. Soc. *54*, 170 (1932).

[29] *D. Britton* and *N. Davidson*, J. chem. Physics *25*, 810 (1956).

[30] *D. Britton, N. Davidson, W. Gehmann,* and *G. Schott*, J. chem. Physics *25*, 804 (1956).

[31] *M. Camac* and *A. Vaugham*, Res. Rep. 84 (AFBMD-TR-60-22) Avco-Everett Lab. 1959.

[32] *J. S. Evans*, Technical Rep. R–92, NASA 1961; *Ch. J. Schexnayder*, Technical Rep. R–108, NASA 1961.

These authors believe that their measurements are accurate within ±20 to ±30 %. *Evans* and *Schexnayder* [32] evaluate their results, without special assumptions as to the reaction mechanism, in terms of $\log k_D = \log A - \frac{B}{T}$. They find, for the region of 5000 to 9000 °K,

$$\lg k_{D(Ar)} = +10.288 - \frac{1.6313 \cdot 10^4}{T}$$

It must be kept in mind that these encouraging results were made possible only by the fact that these reactions have a very simple reaction mechanism.

d 4) Example of an Exothermic Decomposition Reaction

Considerably greater difficulties are encountered in attempts to investigate exothermic reactions. Here chain and chain-branching reactions are to be expected; their quantitative mechanisms can be considered to be accurately known in only a few cases, *e.g.* $H_2 + O_2$ and $H_2 + Br_2$. Therefore, one is frequently limited to statements concerning the over-all course of the reaction. When applying shock waves to exothermically reacting gas mixtures, the mixture to be investigated must usually be diluted with large amounts of an inert gas [*], since, otherwise, as a result of the additional energy produced, self-accelerating shock waves are produced which may in the end lead to a process that is termed detonation (see Section III).

An apparatus with a working principle very similar to that of *Palmer* and *Horning* was recently constructed by *Michel* [33] for investigating the decomposition of hydrazine.

The filter in the experimental setup shown in Fig. 7 was replaced by a small quartz spectrograph. In this way, the variation of the light absorption with time was studied in the wavelength region close to 2300 Å, where N_2H_4 has strong, continuous absorption. Measurements were carried out behind the shock wave that had been reflected at the end of the tube. The gas mixture used consisted of mostly argon, with 0.03 to 0.3 % (by volume) of N_2H_4. Oxygen was carefully excluded. The values of pressure and temperature behind the reflected shock wave were around $P_3 = 3$ -7 atm and $T_3 = 1000$–1500 °K. These were calculated from velocity measurements on the incident shock wave. Since the concentration of hydrazine is very low, the pressure and the temperature behind the shock front can be considered to be constant throughout the reaction zone to a good approximation.

From the shock-wave experiments of *Michel*, a value for the decay time is derived easily. The times that elapse under various conditions until half of the N_2H_4 molecules originally present have decomposed are compared. For constant temperature, one obtains the expression:

$$\tau_{1/2} \sim [N_2H_4]^{1/2}$$

and, referred to a constant concentration of hydrazine at the beginning of the reaction,

$$\tau_{1/2} \approx 10^{-12} \cdot \exp\left(\frac{40000}{RT}\right) \text{ sec}; \quad T = 1000\text{–}1500\ ^\circ\text{K}$$

The relationship between $\tau_{1/2}$ and the hydrazine decomposition mechanism may be complicated. Conclusions can hardly be drawn from these measurements alone. The activation energy measured by *Michel* does not agree with that determined by *Szwarc* [34]. So far, little is known about the mechanism of decomposition of hydrazine. *Szwarc* carried out measurements on the reaction

$$N_2H_4 + 2\,C_6H_5CH_3 \rightarrow 2\,NH_3 + C_6H_5CH_2\text{–}CH_2C_6H_5$$

at low pressures. He determined the variation of the concentration of hydrazine along the axis of a heated tube, through which a gas mixture was flowing. He assumed that the first step during the decomposition of hydrazine is the reaction $N_2H_4 \rightarrow 2\,NH_2$. An energy of activation $E = 60$ kcal/mole was found for this step. *Szwarc* attempted to explain this data by assuming unimolecular decomposition. More recently, *Gilbert* [35] reevaluated *Szwarc*'s measurements critically and came to the conclusion that a bimolecular decomposition scheme explains the data better in the low-pressure region (at which *Szwarc* made his measurements), provided that the non-uniform distribution of temperature in the gas across the cross-section of the tube at the start of its inflow into the hot tube is taken into account. This effect was neglected by *Szwarc*. The rate constant for the reaction $N_2H_4 \rightarrow 2\,NH_2$ therefore becomes

$$k \approx 10^{16} \cdot \exp\left(-\frac{60000}{R \cdot T}\right) \text{ liters/mole/sec}$$

at pressures of less than 1 atmosphere. It is assumed here that a sufficiently rapid further reaction of NH_2 with toluene takes place.

The rate of decomposition $d[N_2H_4]/dt$ of hydrazine at low pressures is found to be approximately proportional to the square of the pressure; this is better adapted to a bimolecular process. Hence, *Gilbert* assumes the following for the initiating reactions:

$$(1)\quad N_2H_4 + M \rightarrow N_2H_4^* + M$$

$$(2)\quad N_2H_4^* + M \rightarrow N_2H_4 + M$$

$$(3)\quad N_2H_4^* \rightarrow 2\,NH_2.$$

The asterisk denotes an energy-rich molecule. The energy is stored in the vibrational degrees of freedom. At low pressures, the rate-determining step in this scheme is reaction (1). This conforms to the well-known reaction mechanism suggested by *Lindemann* [36] and *Hinshelwood* [37] for various decomposition and isomerization reactions of larger molecules, the rate of which at high pressures is proportional to the pressure (first order) and at low pressures to the square of the pressure (second order) (cf. *Rice* and *Ramsperger* [38], *Kassel* [39], and *Slater* [40]).

At present, there are only speculations as to the further reactions of the NH_2 radical during the decomposition of hydrazine. Measurements of the flame velocity [*] at low pressures (30–200 mm) and at 1 atm have indicated practically no dependence of the velocity on the pressure. This

[*] The risk must be run that the inert gas might disturb the reaction mechanism in certain circumstances. In some cases, caution must be exercised in drawing conclusions for undiluted gases from the behavior of diluted mixtures.

[33] *K. W. Michel*, Ph. D. Thesis, Universität Göttingen, 1962.

[34] *M. Szwarc*, Proc. Roy. Soc., Ser. A *198*, 267 (1949).

[35] *M. Gilbert*, Combust. Flame *2*, 137 (1958).

[36] *F. A. Lindemann*, Trans. Faraday Soc. *17*, 598 (1922).

[37] *C. N. Hinshelwood*, Proc. Roy. Soc., Ser. A *113*, 230 (1926).

[38] *O. K. Rice* and *H. C. Ramsperger*, J. Amer chem. Soc. *49*, 1617 (1927); *50*, 617 (1928).

[39] *L. S. Kassel*: Kinetics of Homogeneous Gas Reactions. Chemical Catalog Co., New York, 1932.

[40] *N. B. Slater*, Proc. Cambridge Philos. Soc. *35*, 56 (1939).

[*] The decomposition of hydrazine, *e.g.*, according to the equation: $N_2H_4 \rightarrow N_2 + 2\,H_2$ is an exothermic reaction evolving 26 kcal/mole at 0 °K. Consequently, the appearance of a flame is possible.

indicates that the rate-determining steps of the reaction are of the second order. According to the qualitative relation for the flame velocity $\Lambda \approx \sqrt{\bar{D}/t_R}$, where $\bar{D}$ is the mean diffusion coefficient for active particles in the combustion zone and t_R gives a measure of the time of reaction, it is found that, with $\bar{D} \backsim 1/P$ and $t_R \backsim 1/P$, Λ is independent of the pressure for a second-order reaction.

The dependence of $\tau_{1/2}$ on the temperature T_S found by *Michel*, yields an activation energy of 40 kcal/mole. This quantity is presumably made up of contributions from the initiation reaction (1) with $E \approx 60$ kcal/mole and from succeeding reactions which, at the present, are not fully understood.

Recently, *Britton* and *Cole* [41] investigated the exothermic system hydrogen-bromine in a shock tube. Careful studies at lower temperatures have been made by *Bodenstein* et al. [42,43], which permitted elucidation of the reaction mechanism as well as the relevant reaction rate constants. It is now of interest to investigate the quantitative relationships of the reaction steps at higher temperatures as well.

The essenital reactions are an initiation reaction and recombination reaction:

(1) $Br_2 + M \rightleftarrows 2\,Br + M$

and two chain steps

(2) $Br + H_2 \rightarrow HBr + H$

(3) $H + Br_2 \rightarrow HBr + Br.$

Immediately after bromine atoms have been formed at the start according to (1), reaction (2) becomes rate determining. In their experiments, *Britton* and *Cole* used bromine-hydrogen mixtures, which had been greatly diluted with argon (approximately 1 % H_2, 1 % Br_2, and 98 % Ar). By these means, the temperature change caused by the reaction taking place behind the shock front was kept very small; this facilitated evaluation considerably.

Optical determination of the change of bromine concentration with time, according to the technique applied by *Palmer* and *Hornig*, again proved to be a suitable method of measurement. Table 7 gives a few data from older work in the low-temperature region and data from the shock wave experiments of *Britton* and *Cole*.

Table 7. Reaction between hydrogen and bromine

T [°K]	Author	A [liters/mole/sec]	E_a [kcal/mole]
500—575	*Bodenstein* et al.	5.9×10^9	18.8±0.2
550—600	*Bonhoeffer* [44] et al.	2.15×10^9	18.0±0.7
1300—1700	*Britton, Cole*	3.54×10^9	18.3±1.8
500—1700	(Average)	3.35×10^9	18.3±0.1

The constant k_2 was expressed in the form $k_2 = A T^{1/2} \exp\left(-\frac{E_a}{R \cdot T}\right)$. The values of k_2 obtained at high temperature are in close agreement with those obtained at lower temperatures. However, the experimental accuracy is insufficient to allow distinction between the various theories that go beyond the relatively primitive description afforded by the kinetic theory of gases.

d 5) Techniques for Determining Induction Periods

Another magnitude that can frequently be used to characterize exothermic reactions is the induction period. The induction period is the time interval between the establishment of a steady state behind the shock front and the onset of vigorous reactions. This definition is not unambiguous: the induction period found depends on the sensitivity of the apparatus, and to some extent also on the choice of the property measured. Thus, for example, t_i may often be determined from the appearance of a flash of light associated with the violent start of a reaction, or from the moment when a given concentration of a radical (OH) or a given density gradient is reached. It turns out that all those quantities frequently show a qualitative behavior at the beginning of the reaction similar to that shown in Figure 9.

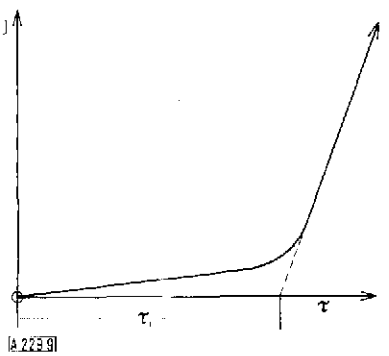


Fig. 9. Increase of various measured quantities J with time at the onset of the reaction (schematic). J = light emission, density gradient, or absorption

Because of the comparatively large variation of the quantity measured within the region t_i, the deviations in the estimate of t_i by the various methods are not excessive. Roughly, one can picture the following situation, for example, in a reaction with chain branching. Within time intervals of the order of t_i, the reaction is accelerated by a combination of radical-formation, chain, and branching reactions. The quantity measured undergoes an approximately exponential rise with time. (The temperature, as approximate calculations show, remains at first practically constant for $t \leq t_i$; the subsequent rise in temperature has an accelerating effect on the reaction.) There will be no great differences between the results obtained with the various experimental procedures, if the limits of sensitivity of the various experimental setups lie in a region in which large changes in the quantities measured occur within a time interval following t_i but small in comparison with the latter; the increase in the quantity measured must be several times the smallest, still measurable value. The methods applied so far have sensitivities which conform approximately to this relationship.

As an example, the measurement of induction periods in mixtures of n-hexane and air performed by *Terao*

[41] *D. Britton* and *R. M. Cole*, J. physic. Chem. *65*, 1302 (1961).

[42] *M. Bodenstein* and *S. C. Lind*, Z. physik. Chem. *57*, 168 (1907).

[43] *M. Bodenstein* and *G. Jung*, Z. physik. Chem. *128*, 127 (1926).

[44] *K. F. Bonhoefer*, *F. Bach*, and *E. A. Moelwyn-Hughes*, Z. physik. Chem. Abt. B *27*, 71 (1931).

[45] can be considered. The apparatus is shown schematically in Figure 10.

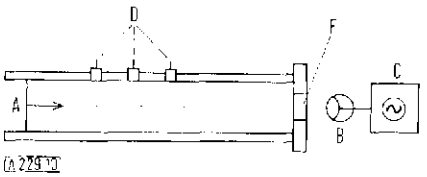


Fig. 10. Experimental setup after *Terao*. The light flash, associated with onset of the reaction behind the reflected shock wave (A), passes through window (F), installed in the terminal flange of the shock tube, and falls on the photocathode of the photomultiplier (B). The velocity of the incident shock wave is measured with the aid of the specially constructed probes (D), which record pressure changes. C = oscilloscope.

The measurements were carried out in the reflected shock wave. The oscilloscope simultaneously records signals from the probes used in determining the velocity of the incident shock wave and from the photocell which detects the light flash occurring after reflection of the shock wave. From these data the time elapsing between the appearance of the shock front and the emission of the light flash after the start of the reaction in the reflected shock wave can be calculated. This time is called the "induction period."

Some of the measurements are shown in Fig. 11. Further induction period data for lower temperatures (600–700 °K), obtained by *Martinengo* and *Wagner* [46] by a different method (adiabatic compression), are of interest and are also

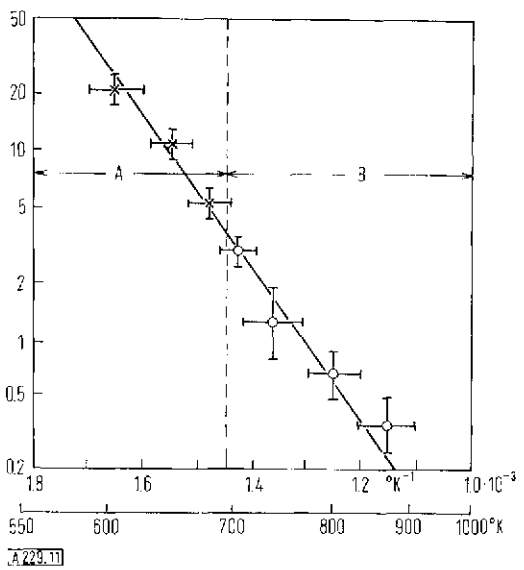


Fig. 11. Induction period as a function of the reciprocal of the absolute temperature $1/T$ or of the absolute temperature T for n-hexane-air mixtures. A) region of adiabatic compression; B) shock-wave experiments. The straight lines through the points denote the extent of experimental variation. Ordinate: induction period τ_i (msec), Abscissa: top: reciprocal of absolute temperature [°K⁻¹], bottom: absolute temperature [°K].

included. It is seen that with t_i values on the logarithmic scale, a straight line fits the data quite well over a span of two orders of magnitude. These data can be expressed by the equation:

$$t_i \approx 10^{-3} \exp\left(\frac{E}{R \cdot T}\right) \text{sec}$$

E = 17.4 kcal/mole

for an n-hexane-air mixture with 1.74 % by volume of n-hexane. Temperature between 600 and 900 °K.

[45] *K. Terao*, personal communication.

[46] *A. Martinengo, H. Gg. Wagner*, and *D. Zunft*, Z. physik. Chem. N. F. *22*, 292 (1959).

E. Schmidt [47] has reported similar experiments on mixtures of hydrocarbons and air. However, the results have not yet been published. *Garvin* and *Plooster* [48] studied the induction period of mixtures of bromine and hydrogen.

Measurements on the system hydrogen + oxygen have been undertaken by *Steinberg* and *Kaskan* [49], as well as by *Schott* and *Kinsey* [50]. As the controlling variable for determining the induction period, the latter authors used the attainment of a given OH concentration, found by tracing the course of absorption in the OH band system near 3064 Å. It is to be hoped that this method, in which the formation of a specific type of particle is followed, will yield information concerning the individual steps of the reaction mechanism.

e) Means for Extracting a Sample from behind a Shock Wave

Hertzberg and *Glick* [51] and *Hertzberg, Glick*, and *Squire* [52] have described an apparatus which regulates the phenomena of flow in the shock tube in such a manner that the gas in the tube is kept at a constant temperature T throughout a certain period (order of magnitude of milliseconds) and is then cooled rapidly by a rarefaction wave. Following this, samples can be removed and analyzed chemically by any appropriate technique. The reaction kinetics can thereby be studied if the reaction is not permitted to reach equilibrium during the time in which the gas mixture is kept at temperature T.

This method appears to be especially suitable for studying reactions with high activation energies, where the reaction rate drops considerably even with a comparatively small decrease in temperature. A diagram of the apparatus is given in Figure 12. The flow phenomena in the shock tube are shown qualitatively on a distance *vs.* time diagram in Figure 13.

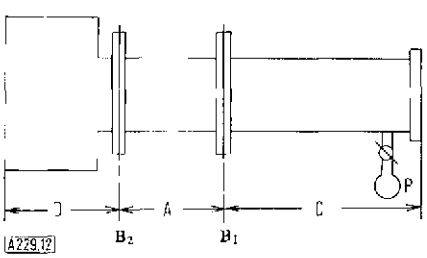


Fig. 12. Apparatus according to *Hertzberg, Glick*, and *Squire*. A and C denote the driving and shock tubes, respectively, as described earlier. The novelty here is the addition of a large container D evacuated prior to the experiment and separated from the driving tube A by a second membrane or diaphragm B_2. P is an evacuated vessel with a stopcock, into which a sample of the reacted gas mixture from C is introduced for analysis. A short time after the membrane B_1, has been punctured, the membrane B_2 is ruptured. A strong rarefaction wave, which rapidly cools the gas behind the shock front in C, is generated by the flow into vessel D.

[47] *E. Schmidt*, Brennstoff, Wärme, Kraft *10*, 295 (1958).

[48] *D. J. Garvin* and *M. Plooster*, J. Amer. chem. Soc. *78*, 6003 (1956).

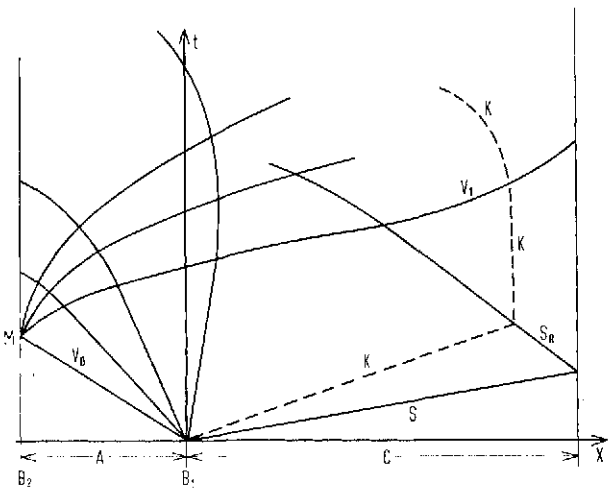
[49] *W. E. Kaskan* and *M. Steinberg*, 5th Symposium on Combustion. Chapman and Hall, London 1955, p. 664.

[50] *G. L. Schott* and *J. L. Kinsey*, J. chem. Physics *29*, 1177 (1958).

[51] *A. Hertzberg* and *H. S. Glick:* Fundamental Data obtained from Shock Tube Experiments. AGARDOgraph 41, Pergamon Press, London 1961.

[52] *A. Hertzberg, H. S. Glick*, and *W. Squire*, 5th Symposium on Combustion. Chapman and Hall, London 1955, p. 393.

A characteristic of this arrangement is the strong rarefaction wave V_I caused in container D by the flow of gas from A after rupture of the membrane B_2. This effects: 1) faster cooling of the gas compressed in C by the shock waves S and S_R (in comparison with a "normal" shock tube) and 2) a predetermined direction of motion of the gas towards the container



A 229 13

Fig. 13. Qualitative distance *vs.* time diagram of the flow phenomena in the shock tube of *Hertzberg* and *Glick*. By suitable choice of the starting conditions, it is possible to control the process in such a way that the reflected shock wave S_R passes through the contact interface K without generating a second shock or rarefaction wave along the positive x-direction at that point. Furthermore, it is possible to guide the flow of the gas in the direction of container D after the rarefaction wave V_I overtakes the contact interface area. Attention is drawn to the trace of contact interface K in the upper part of the figure. According to [51]. At M: rupture of membrane B_2.

D after the rarefaction wave V_I has overtaken the contact interface K. If these measures are not taken, the analysis of the gas mixture from the tube C may be disturbed by gas from the driving tube A, which can sometimes reach the sampling area at the end of the shock tube (for example, at position x_1) during the pressure equilibration period.

Shock waves which enter container D (for instance, S_R) are very strongly attenuated there, and, since the flow at the opening between A and D attains approximately sonic velocity during the expansion of gas from A into D, the shock waves reflected from the rear wall of D are unable to escape from that vessel. Disturbances accompanied by small pressure changes propagate almost at the velocity of sound. The tube positions at which the flow reaches sonic velocity cannot be passed by small disturbances. Theoretical studies of processes in this type of shock tube [13, 53, 54] show that if the shock wave S_R is to pass through the contact interface K without generating secondary disturbances, the product of density and sound velocity must be the same on both sides of the contact interface prior to the impact of the S_R wave. This can often by accomplished by adjusting the composition of the gases in the driving tube A. By this means, rapid and undisturbed cooling of the gases heated by S_R is obtained. In the "normal" shock tube, however, the rate of cooling is slower. The cooling is interrupted by repeated periods of heating, each of decreasing intensity, even when interaction of S_R and K is prevented. This phenomenon is caused by the reflection of S_R by the end x_0 of the driving tube A, the resultant shock wave being reflected again at x_1, and so on (cf. Fig. 3).

The method of *Hertzberg*, *Glick*, and *Squire* contains several sources of error that must be considered in its application. 1) First, the gas mixture to be investigated is preheated by the incident shock wave S. In certain circumstances, the possibility of initiation of a reaction in that mixture must therefore be considered. 2) The temperature of reaction T_3, which is produced by the reflected shock wave, is maintained in the gas mixture for varying lengths of time. Gas particles at the end of the tube (x_1) are subjected to T_3 for longer periods of time than particles in the vicinity of the contact interface. 3) Finally, cooling of the gas mixture by the rarefaction wave V_I requires a finite time during which the composition of the mixture can undergo changes. Reactions that are strongly dependent on temperature (high energy of activation) are influenced to a relatively small degree by effects (1) and (3). By a proper choice of the ratio of the driving and the shock tube lengths, and of the absolute length of the shock tube as well, the error caused by effect (2) can be reduced too.

Hertzberg, *Glick*, and *Squire* first investigated the reaction between nitrogen and oxygen at high temperatures (2000–2800 °K). The rate of conversion is strongly dependent on the temperature, which would seem to indicate that the method is relatively suitable for study. The experiments were first evaluated with the probably not very good assumption of the following, very simple reaction steps:

$$\text{(1)}\quad N_2 + O_2 \xrightarrow{k_1} 2\,NO \qquad \Delta H\ (2500\ °K) = 43\ \text{kcal/mole}$$

$$\text{(2)}\quad 2\,NO + M \xrightarrow{k_2} N_2 + O_2 + M \qquad -43\ \text{kcal/mole}$$

In these experiments, M was krypton or argon. Integration of the equation for the rate of formation of NO according to this mechanism, using,

$$\frac{d\,[NO]}{dt} = k_1\,[O_2]\,[N_2] \cdot k_2\,[M]\,[NO]^2$$

yielded a simple expression:

$$\sqrt{[O_2]_0[N_2]_0} \cdot K_c\,[M] \cdot k_2 \cdot \Delta t \approx \ln \frac{[NO]_{eq.} + [NO]\,\Delta t}{[NO]_{eq.} - [NO]\,\Delta t}$$

where $[O_2]_0$ and $[N_2]_0$ are the initial concentrations of oxygen and nitrogen behind the reflected shock wave; K_c is the equilibrium constant

$$K_c = \frac{[NO]}{[O_2]^{1/2}\,[N_2]^{1/2}}$$

Δt is the time during which the mixture was kept at the temperature of reaction; $[NO]_{eq.}$ is the concentration at equilibrium; and $[NO]_{\Delta t}$ is the concentration determined analytically. It was ensured that $[NO]_{eq.} \ll [O_2]_0$ and $k_1 \ll k_2$ at the reaction temperature. Evaluation of the data according to this mechanism showed that k_2 is a function of the oxygen concentration *viz.* $k_2 \sim 1/[O_2]^{1/2}$, whereas changes in the nitrogen concentration had no effect. The energy of activation for k_2 was determined to be 92 + 5 kcal/mole. From this an energy of activation of 135 ± 5 kcal/mole for reaction (1) can be calculated. The dependence of k_2 on the oxygen concentration indicates that the reaction mechanism assumed is not correct. A revised evalution, using a chain mechanism, which was first suggested by *Bodenstein* [55] and later by *Zeldovich* [56], agreed better with the experimental data.

[53] *S. Paterson*, Proc. Roy. Soc. *61*, 119 (1948).

[54] *L. G. Napoltiano:* Fundamental Data obtained from Shock Tube Experiments. AGARDOgraph 41, Pergamon Press, London 1961.

[55] *M. Bodenstein*, Roczniki Chem. *18*, 374 (1938); Chem. Abstr. *33*, 6534 (1939).

[56] *Y. B. Zeldovich*, Acta Physicochim. U.S.S.R. *21*, 577 (1946); see also *E. Freedmann* and *J. W. Daiber*, J. chem. Physics *34*, 1271 (1961).

The initiation reaction

(3) $M + O_2 \rightarrow 2O + M$

generates oxygen atoms, which react further according to

		ΔH at 2500 °K
(4)	$O + N_2 \rightarrow NO + N$	76 kcal/mole
(5)	$N + O_2 \rightarrow NO + O$	−32.5 kcal/mole

The experimental data indicate that the respective equilibrium concentrations of O and NO are established at a faster rate in reaction (3) than in the formation of NO [*]. These data therefore justify the assumption of an approximately steady-state oxygen concentration during the formation of NO. Assuming also that $[NO] \ll [O_2]$, a simple expression for the rate of formation of NO during the initial stage of the reaction can be derived:

$$\frac{d[NO]}{dt} \approx \frac{2K_{O_2}}{[O_2]^{1/2}} \cdot k_4 \cdot [O_2] \cdot [N_2] \quad \text{and} \quad K_{O_2} = \frac{[O]}{[O_2]^{1/2}} \quad \text{at equilibrium}$$

If we assume that

$$k_1 = \frac{2K_{O_2} \cdot k_4}{[O_2]^{1/2}}$$

then with

$$k_2 = \frac{k_1}{K_{NO}} \quad \text{where} \quad K_{NO} = \frac{[NO]^2}{[O_2][N_2]} \quad \text{also at equilibrium}$$

we obtain the dependence of k_2 on the oxygen concentration

$$k_2 = \frac{2K_{O_2}}{K_{NO}} \cdot \frac{k_4}{[O_2]^{1/2}} \sim \frac{1}{[O_2]^{1/2}}$$

as found experimentally. The activation energy of reaction (4) amounts to 74 ± 5 kcal/mole.

The measurements by *Zeldovich* agree well with the experimental results discussed here. The activation energy of reaction (5) has been determined by *Kaufmann* and *Kelso* [57].

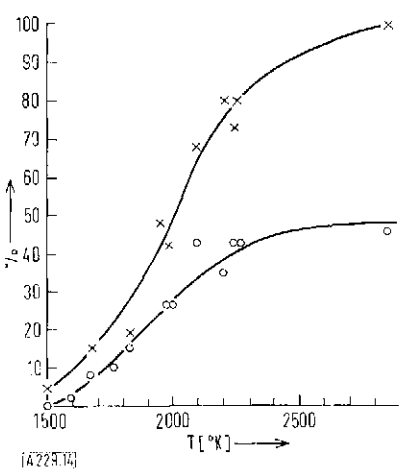


Fig. 14. Pyrolysis of methane. The conversions of methane into acetylene and ethylene are shown for a constant reaction time (about 1 msec) as functions of the temperature behind the reflected shock wave S_R (after [51]).
x = % CH_4 decomposed
o = % CH_4 converted into C_2H_2 and C_2H_4

[*] This can be estimated from the measurements of the rate of dissociation of oxygen at high temperatures cited earlier.

[57] *F. Kaufmann* and *J. R. Kelso*, J. chem. Physics *21*, 751 (1953).

Hertzberg and *Glick* have investigated the pyrolysis of methane and the reaction between hydrocarbons (butane, ethane) and water vapor at high temperatures with a similar apparatus. Some of their results are reproduced in Figures 14 and 15.

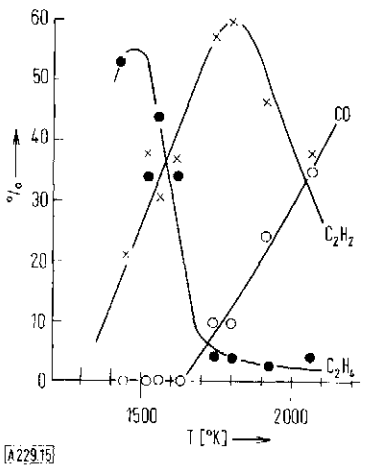


Fig. 15. Reaction of butane with water vapor. The starting mixture consisted of 1.04 % by volume of C_4H_{10}, 16.6 % by volume of H_2O, and 82.4 % by volume of Ar + Ne. The quantities of the products formed are shown as functions of the reaction temperature at approximately constant reaction time (1 msec) (after [51]).

f) Measurement of the Dissociation Energy of Nitrogen Using Shock Waves

In this section, certain applications of shock waves that are not directly concerned with chemical kinetics will be discussed. A prerequisite for kinetic investigations is knowledge of thermodynamic data for the substances participating in the reaction. In general, this data is fairly complete nowadays, except for unstable intermediate products, radicals, and the like (for example HCO, CH_3). Up to a few years ago, the exact energy of dissociation of nitrogen was unknown, since the usual thermal methods failed because of its large value. On the other hand, evaluation of the band spectra of nitrogen indicated two values of D_0, *viz.* 7.37 and 9.76 ev, with no clear decision as to the correctness of either one.

Toennies and *Greene* [58] and *Christian, Duff*, and *Yarger* [59] utilized shock waves in nitrogen for determining D_0. The high temperature of $T \geq 4000$ °K required for a significant dissociation into atoms can easily be reached with shock waves. *Christian* et al. used suitable explosives for the generation of shock waves. These experiments will not be described here, as they can be performed in only few laboratories. Instead, the measurements of *Toennis* and *Greene*, who used a standard experimental setup, will be discussed in some detail. They measured the velocities of the incident and the reflected shock wave. The temperature behind the incident shock wave was still insufficient here for a significant dissociation of nitrogen. Using the data obtained for the

[58] *J. P. Toennies* and *F. E. Greene*, J. chem. Physics *26*, 655 (1957).

[59] *R. H. Christian, R. E. Duff*, and *F. L. Yarger*, J. chem. Physics *23*, 2045 (1955).

velocity of the incident shock wave and each of the two dissociation energies in question in turn, the corresponding velocity of the reflected shock wave was calculated and compared with the experimental results. Satisfactory agreement between the measurements and calculation was obtained only for the higher value of the energy of dissociation, $D_0 = 9.76$ ev. Figure 16 shows a sketch of the experimental apparatus.

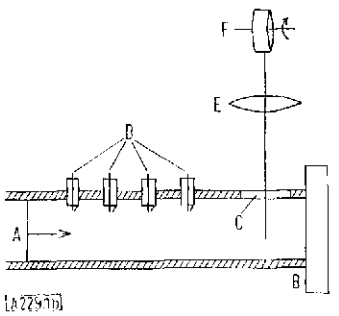


Fig. 16. Experimental apparatus according to *Toennies* and *Greene*. Measurement of the velocity of the incident shock wave (A) was carried out with ionization probes (D) (cf. page 194). Four observation points were installed at which signals were recorded on an oscilloscope. The heated gas behind the reflected shock wave emitted so strongly that the wave could be photographed with a camera F, equipped with a rotating film drum. The gas in the high-pressure section consisted of H_2 (up to 50 atm); the initial pressure of nitrogen in the shock tube was 0.5 to 10 mm Hg. B) Terminal flange; C) window; E) lens.

Evaluation of the photographs obtained with the rotating drum camera indicated that, immediately after reflection of the shock wave from the terminal flange, there is a short period of wave acceleration before a constant velocity is attained. *Toennies* and *Greene* ascribe this to vibrational relaxation effects in the nitrogen molecules behind the incident shock wave.

The accuracy of the measurements of the velocity of the reflected shock wave was only within $\pm 10\,\%$. This was absolutely sufficient, however, to decide which of the two values of the dissociation energy of nitrogen is determinant during thermal dissociation.

g) Experiments for Measuring Rotational Relaxation of Diatomic Molecules Using Shock Waves

In practically all cases, the time required to establish equilibrium between the rotation and translation of di- and polyatomic molecules is comparable to the time required for the attainment of an equilibrium distribution of translation of the individual molecules. It can be assumed that equilibrium of translation and rotation is established after an average of approximately five to twenty collisions per molecule. Chemical reactions take place much more slowly; therefore, this effect does not have to be considered in computing the temperature behind the shock front prior to the start of reaction. (Vibrational relaxation of di- and polyatomic molecules can, however, exert an important influence. Measurement of this relaxation time can be carried out readily with ultrasonic waves of small amplitude and frequencies in the range of 1 kilocycle to approximately 1 Mc.) In order to measure rotational relaxation frequencies above 10 to 15 Mc are required, and these have only very recently become available for such purposes.

There is a method due to *Hornig*, *Greene*, and *Cowan* [24] that permits definite conclusions to be drawn about the course of the density increase in shock fronts by determining the light reflection at these fronts. As soon as the rotational relaxation time significantly exceeds the translational relaxation time, a density profile of the shock front such as that shown in Fig. 17 should be expected.

For the limiting case, in which region 2 is much longer than region 1, the intensity of the reflected light is determined almost solely by the density jump in region 1. A density jump such as that seen for monatomic gases would then be observed. If the conditions in the shock front are now changed in such a manner as to shorten the rotational relaxation time, whereby region 2 becomes comparable to region 1, then the intensity of the reflected light will depend increasingly on region 2 as well. Correspondingly, the density jump measured will be larger than that observed in a monatomic gas.

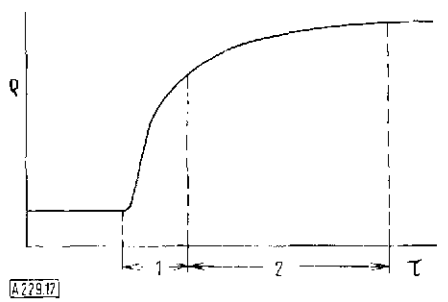


Fig. 17. Qualitative course of the density increase in a shock front with rotational relaxation
1: equilibration of translation
2: equilibration of rotation

This case gives us a measure of the number of collisions that are required on the average to establish thermodynamic equilibrium between translation and rotation. With certain assumptions, this value can be converted into the number of collisions that a molecule must experience on the average, in order to transfer energy that is just sufficient for one rotational quantum. Fig. 18 shows a diagram of the experimental apparatus used by *Hornig* et al.

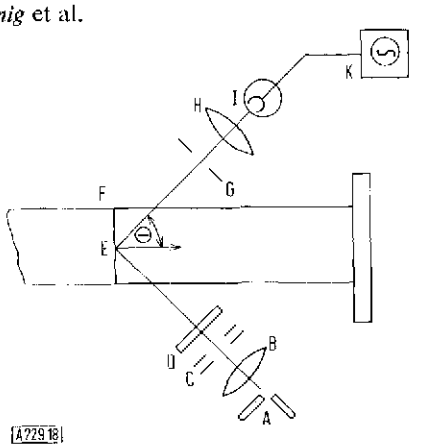


Fig. 18. Apparatus for measuring light reflection at shock fronts. A carbon arc (A) serves as light source. An approximately parallel beam of light is formed by the combination of slit (C) and filter (D); the light beam impinges on the shock wave (E) at an angle of incidence Θ ($\Theta \approx 60$–$80°$). A photocell (I) records the fraction of the light reflected and sends the signal into an oscilloscope (K). B) Lens; F) glass tube; G) slit; H) lens.

The variation of the refractive index in the shock front (Mach number 1 to 1.5) is fairly small, even at relatively high initial pressures ($P_0 \geq 1$ atm). The reflection coefficient amounts only to approximately 10^{-4} to 10^{-7}. This can be deduced easily from Fresnel's formulas by assuming purely discrete variations in the index of refraction. To a second approximation, the reflection coefficient R can be represented as a function of the finite thickness of the shock front; R then becomes dependent on the angle of incidence Θ, on the total change in the index of refraction Δn, and on the wavelength λ of the light used. The latter dependence is a consequence of the comparable magnitudes of the thickness of the shock front and the wavelength of light in the visible region. The theory of light reflection at shock waves cannot be discussed further here; the reader is referred to original articles by *Cowan*, *Green*, and *Hornig*.

Hornig et al. carried out measurements in various gases, in which the angle of incidence Θ and the wavelength of the light used were varied between 60 and 80° and 4500 and 7000 Å, respectively, at constant Mach numbers. In this way, variations of the index of refraction in the shock front could be determined to within about ±20 %. The measured data are conveniently expressed in terms of a characteristic length L, which is defined as follows:

$$L = \frac{\Delta n}{\left(\frac{dn}{dx}\right)_{max}} \quad \text{where}$$

Δn = change of index of refraction in the shock front

$\left(\frac{dn}{dx}\right)_{max}$ = maximum value of the gradient of the index of refraction in the shock front

L is compared with a value calculated theoretically for which the assumption of complete equilibrium between translation and rotation is made. The vibrational motion remains virtually "frozen". In the region of small Mach numbers (1–1.4), the results agree well with the shock front theory for weak shocks, according to *Mott–Smith* [79] and *Wang–Chang* [80]. A rotational relaxation time appreciably exceeding the translational relaxation time has not been measured so far. According to early investigations by *Cowan*, *Greene*, and *Hornig* [24], nitrogen appeared to require a significantly longer time for the excitation of rotation; however, in more recent work using an improved arrangement, *Andersen* and *Hornig* [25], did not observe such an effect [*].

The number of collisions needed to establish just 1/e of the final value of the index of refraction for equilibrium between rotation and translation was found to be $Z^* \approx 1.5$–2. This applies for the gases N_2, O_2, CO, N_2O, CO_2, CH_4, NH_3, HCl, and Cl_2, which have been investigated so far. The rise in temperature in the shock wave with the gases lay between 100 and 140 °K. Hydrogen behaved like a rare gas at the experimental temperature because of its relatively large rotational quanta compared to kT. The transition of energy from translational into rotational (and vibrational) motion occurs only in an extended zone behind the shock front which cannot be encompassed by the method of light reflection.

With nitrogen, according to measurements by *Anderson* and *Hornig*, the possibility cannot be completely excluded that, only approximately 93–95 % of the energy required for rotation is transferred within the shock front, because here, too, the rotational quanta are relatively large in comparison with kT within the temperature region investigated.

[*] Measurements by *Greenspan* [26], who used the method of ultrasonic dispersion (applying frequencies of up to 12 Mc), indicated that approximately four to five collisions are required to transfer 1/e of the rotational energy in nitrogen. Similar results were obtained by *Zmuda* [60], *Keller* [61], and *Boyer* [62].

[60] *A. Zmuda*, J. acoust. Soc. America *23*, 472 (1951).

[61] *K. H. Keller*, Physik. Z. *41*, 386 (1940).

[62] *R. Boyer*, L. acoust. Soc. America *23*, 176 (1951).

III. Detonations

In the following, a phenomenon will be considered which has a certain relationship to shock waves and which occurs in sufficiently fast, strongly exothermic reactions.

a) Properties of Detonations

A "steady-state detonation" is the designation given to a combustion process which propagates into unburnt gas with a large velocity independent of time (1000–4000 m/sec). During the last few years, investigations have shown that during this process, the fresh gas is compressed and heated by a shock wave and that thereafter, it reaches within a comparatively thin zone conditions very close to thermodynamic equilibrium. The thickness of the combustion zone is independent of time for detonations with constant velocities, *i.e.* for steady-state detonations.

We shall forego a theoretical treatment here. The reader will find detailed accounts, for example, in articles by *Jost* [3], *Lewis* and *von Elbe* [6], and *Zeldovich* and *Kompanets* [63]. Some results of the theory are merely given without derivation. The velocity of steady-state detonations can be calculated – assuming a very fast chemical reaction and without special knowledge of the mechanism of the latter – from the laws of conservation of mass, momentum, and energy, the gas equation, the thermodynamic data for the burning gas, and one additional condition, named after *Chapman* and *Jouguet* [3,6,63]. The latter states that, seen from the position where chemical equilibrium is completely established [*] in the burnt gas, the front of a steady-state detonation propagates at precisely the velocity of sound for the combusted gas. Weak disturbances that originate in farther removed regions of the burning gas cannot therefore penetrate into the zone of chemical conversion. In recent years, some objections pertaining to the choice of the "correct" sound velocity that is to be operative for the stabilization of detonation in the Chapman-Jouguet front have been raised, mainly by *Kirkwood* and *Wood* [64]. By reasoning from basic considerations, they came to the conclusion that the velocity of sound for a completely "frozen" chemical equilibrium and arrested vibrational and rotational degrees of freedom is the pertinent one.

Apart from the difficulty of imagining how the propagation of real disturbances in the reacted gas at such a sonic velocity is supposed to occur, experiments by *Wagner* and *Homann* [65] on detonations in very thin paper tubes, in which such an effect would have an

[63] *Y. B. Zeldovich* and *A. G. Kompanets*: Theory of Detonations. Academic Press, New York 1960.

[*] The assumption of a completely attained equilibrium is a simplification, since equilibrium can be reached only after an "infinitely" long time. The experimental measurements were, however, in very good agreement with theoretical values for the detonation velocity calculated using this assumption.

[64] *J. G. Kirkwood* and *W. Wood*, J. appl. Physics *28*, 395 (1957).

[65] *H. Gg. Wagner* and *K. Homann*, unpublished.

opportunity to occur because of the very rapid pressure drop behind the detonation front, showed no deviation of the detonation velocity that might indicate any involvement of sonic velocity in frozen equilibria. In this connection, some arguments have been advanced by *Wagner* [66] that support the stabilization of detonations by the formation of a boundary layer in the flow behind the detonation front. This cannot be discussed at length here, since it would exceed the scope and the purpose of the present article. With regard to this subject, the reader is refered to a paper by *Wagner* to be published shortly.

Phenomena occurring in the reaction zone of a detonation may be represented qualitatively by a pressure *vs.* density diagram (Fig. 19). The curves a and b result from a suitably

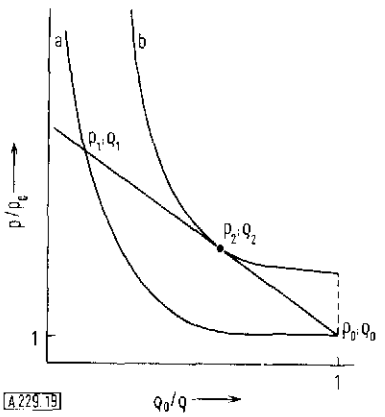


Fig. 19. Phenomena in the reaction zone of a detonation. The figure shows the possible values of the pressure and density that a shock wave may produce discontinuously starting from the initial gas state (P_0; ϱ_0) without a chemical reaction (Curve a). Curve b shows the possible final values of the pressure and the density after the chemical reaction has proceeded to equilibrium. For a steady-state detonation, the values designated by (P_1; ϱ_1) and (P_2; ϱ_2), respectively, are selected by the Chapman-Jouguet condition.

transformed of the energy equation, which here is also called the Hugoniot equation. The possible states that can be attained by a shock wave starting from P_0; ϱ_0 are given by

$$h_1 - h_0 = \frac{1}{2}(P_1 - P_0)\left(\frac{1}{\varrho_0} + \frac{1}{\varrho_1}\right)$$

h = enthalpy per gram of gas mixture
P = pressure
ϱ = density

If the change of enthalpy caused by the chemical reaction is added to the left hand side, the Hugoniot equation for the final values of pressure and density after occurrence of the chemical reaction is obtained (Curve b in Fig. 19).

Theory states that, in steady-state detonation, variations in the values of P and ϱ follow the straight line c after the initial compression by the shock wave to P_1 until the equilibrium values P_2 and ϱ_2 are reached. The absolute value of the slope of this straight line, which starts from P_0, ϱ_0 and is tangent to curve b at P_2, ϱ_2 is proportional to the square of the steady-state velocity of the detonation (Rayleigh linie).

$$\frac{P_2 - P_0}{\frac{1}{\varrho_0} - \frac{1}{\varrho_2}} = \varrho_0^2 D^2$$

From Fig. 19, the variation of the parameters of the equation of state in the zone of the chemical reaction can be derived qualitatively as a function of time or distance from the shock front. An observer moving with the detonation front will see the relationship as presented in Fig. 20.

[66] *H. Gg. Wagner*, unpublished.

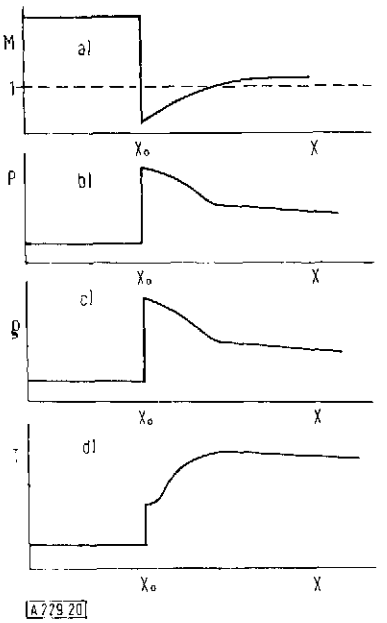


Fig. 20. A moving observer X_0 sees the flow (a) approaching him at a Mach number $M > 1$. After passage through the shock-wave front, the Mach number drops suddenly to less than 1 and then, as the chemical reaction progresses, approaches the value 1 in the "Chapman-Jouguet" plane. The Mach number is defined here as the ratio of the flow velocity to the local sound velocity. The qualitative variation of pressure, density, and temperature in the zone of chemical conversion is shown in the following diagrams (Figs. 20b to d).

Determination of the variations of the density in the reaction zone will be described further below. The possibility of applying steady-state detonations to problems in reaction kinetics will now be discussed.

b) Production of Detonations

Detonations can be initiated in numerous gas mixtures in which a strongly exothermic reaction is able to proceed. The usual method is ignition with a spark or – what proves to be better in a number of cases – by means of a triggering detonation using a gas mixture which detonates especially well (*e.g.* 2 C_2H_2 + 3 O_2; 2 H_2 + O_2). The same arrangement as that shown in Figure 1 may be used. The initial detonation breaks the thin membrane B and triggers the detonation to be investigated in tube C. However, here rather long transient distances are to be expected. Depending on the conditions, the detonation becomes steady only after travelling 30 to 150 tube diameters.

The thickness of the reaction zone becomes a useful quantity for kinetic measurements only if the detonation proceeds into a gas at low pressure (P_0 $<$200 mm Hg). In this case, the thickness of the reaction zone is of the order of 0.5 to 1 cm, and measurements can be made within it, whereas in steady-state detonations at atmospheric pressure, the reaction zones are only 10^{-1} to 10^{-2} cm wide. The temperatures and pressures at the end of the reaction zone lie in the range $T \approx$ 3200 to 4000 °K and $P \approx$ 0.5 to 16 atm, depending on the initial conditions. Thus, it is possible to investigate reactions under fairly extreme conditions. The experiments which have been carried out so far involved measurements of the change of

density, the "reaction time", the "induction time", and the variation of the OH concentration within the reaction zone in detonations of hydrogen-oxygen and hydrocarbon-oxygen mixtures.

c) Measurement of Induction Periods of Detonations

The simplest and the most useful method of measurement proved to be the determination of the gradient of the index of refraction, using schlieren techniques.

The experimental setup is quite similar to that shown in Fig. 4. Here exactly one half of the image of the slit is covered by means of a shutter. Analogous to the changes in density shown in Fig. 21 (see page 209), deflection of the light in opposite directions is obtained because the density gradients within and behind the shock front, respectively, are of different signs. The photocell records on the one hand an increase, and on the other, a decrease in the incident light intensity.

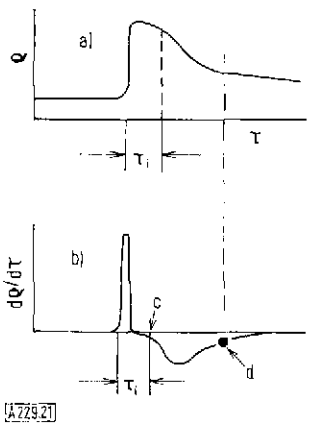


Fig. 21. Diagram (a) shows the qualitative changes of the density in the reaction zone of a steady-state detonation as a function of time τ, with the observer at rest. Diagram (b) shows the derivative of density with respect to time *vs.* time τ.

In Fig. 22, the values of τ_i for $H_2 + O_2$ and n-hexane + O_2 detonations, measured by *Just*, *Luig*, and *Wagner* [67], and by *Just*, *Pusch*, and *Wagner* [68], are plotted as functions of concentration. The initial pressure of the fresh gas was 110 and 150 mm Hg for $H_2 + O_2$ and n-hexane + O_2, respectively. It is of interest to note that

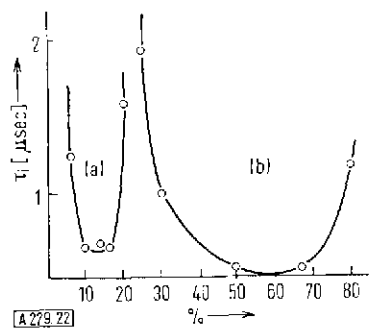


Fig. 22. Measurements of the induction period of $H_2 + O_2$ (b) and n-hexane + O_2 (a) detonations *vs.* the fuel concentration. The times refer to an observer at rest. The initial pressures P_0 of the mixtures were 110 and 150 mm Hg, respectively.

[67] *Th. Just, F. J. Luig*, and *H. Gg. Wagner*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *65*, 403 (1961).

[68] *Th. Just, W. Pusch*, and *H. Gg. Wagner*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *65*, 410 (1961).

there is a sharp increase of τ_i in the vicinity of the detonation limits. Presumably, the appearance of detonation limits is closely related to this. For comparison, Fig. 23 shows measurements of the limits of detonation for various mixtures by *Schüller* [69], *Wendtland* [70], and *Breton* [71]. The initial pressure was 1 atm.

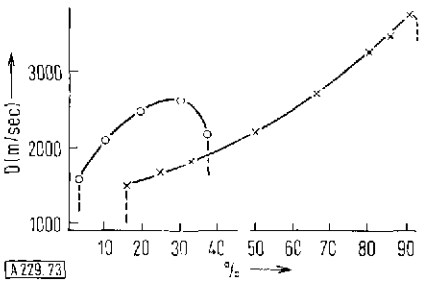


Fig. 23. Velocities of steady-state detonations of various mixtures as a function of the fuel concentration. The process becomes discontinuous at the limits, which are indicated by dotted lines. Outside the limits, a flame runs through the tube. x: $H_2 + O_2$; o: $C_3H_8 + O_2$; abscissa: % fuel.

It must be carefully ascertained during these measurements that in the neighborhood of the limits actually a steady-state detonation is observed. All the authors used well-detonating mixtures for the imitation of their detonations. The influence of the initial detonation can be safely excluded only if the experimental tube is sufficiently long. In general, this requires tubes many meters long. Velocity measurements must be carried out over long distances. This is the only proof that a detonation is stationary.

A steady-state detonation is sustained within the limits; outside the limits, a flame runs through the tube. The transition from one phenomenon to the other takes place discontinuously within a very small range of concentration. The sharp increase of the induction period and the reaction time in the vicinity of the limits leads to the surmise that the effect of heat losses to the walls of the tube is no longer negligible and that this effect finally becomes so large that a steady-state detonation cannot be maintained. *Just* and *Wagner* [72] obtained estimates in good approximation of the position of the detonation limits for oxygen-hydrogen mixtures from the measured dependence of the induction period on the temperature just behind the shock front, and the influence of heat losses to the walls. As long as the tube diameter is not too small (< 1 cm), its influence on the detonation limits is extremely slight.

The mechanism of the $H_2 + O_2$ reaction is fairly well known in detail from numerous earlier investigations. Here it proved successful by using the dependence of the induction period on the initial temperature behind the shock front to determine activation energies of some single reaction steps, *viz.*:

$$H + O_2 \xrightarrow{k_1} OH + O \quad \text{and} \quad O + H_2 \xrightarrow{k_2} OH + H$$

The method used to evaluate the experiments will be treated only briefly here. It is described in more detail in the paper by *Just, Luig*, and *Wagner* [67]. A beam of light normal to the gradient of the index of refraction (Fig. 24) is deflected through a small angle δ, which is proportional to the length of the light path A and to the gradient:

$$(2) \qquad \delta = A \cdot \frac{dn}{dy}$$

[69] *H. W. Schüller*, Ph. D. Thesis, Technische Hochschule, Darmstadt 1954.

[70] *R. Wendtland*, Z. physik. Chem. *110*, 637 (1924); *116*, 227 (1925).

[71] *M. J. Breton*, Ann. Off. nat. Comb. liquides *11*, 487 (1936).

[72] *Th. Just* and *H. Gg. Wagner*, unpublished.

For an observer moving at the velocity of detonation:

$$(3)\quad \frac{dn}{dy} = \frac{dn}{dt}\Big/u(t)$$

where u is the velocity of the gas flow behind the shock front as seen by an observer moving with the front. An observer moving with the detonation front observes the gas

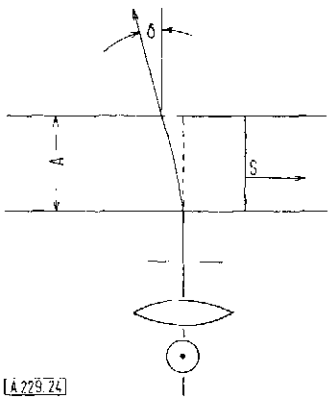


Fig. 24. Deflection of a narrow beam of light by a refractivity gradient behind the shock front S. A) Internal diameter of tube.

coming towards him at the detonation velocity; after compression by the shock wave, he sees it moving away with a velocity u. The latter depends on the phenomena in the adjacent reaction zone, and thereafter on cooling processes and other factors (cf. Fig. 20). The transformation of the time t of the observer in motion into the measur time τ of the observer at rest is performed according to page 195. Since the time t is relevant for the reaction kinetics, one must now attempt to establish a relationship between the expression

$$(4)\quad \delta = A \cdot \frac{1}{u} \cdot \frac{dn}{dt}$$

and the variation of density. In accordance with the statements on page 195, Eq. (1) is used for that purpose and gives, approximately,

$$5)\quad \delta \approx A \cdot \frac{1}{u} \cdot \frac{\Sigma x_i \alpha_i}{m} \cdot 2\pi \cdot \frac{d\rho}{dt}$$

Since conversion is small at the beginning of the reaction, it is assumed that the average molar polarization $\Sigma x_i\alpha_i$ is approximately constant. The same holds, to a good approximation, for the average molecular weight, since the number of particles remains nearly constant during the initial stage, because of the preponderance of bimolecular reactions (cf. below). The variation of the density behind the shock front is caused by the evolution of heat at the onset of the reaction. According to the statements on page 206, the parameters P and ρ behind the shock front in a steady detonation vary along a straight line (Rayleigh line) in the P *vs.* ρ diagram. After a lengthy computation, the following expression is obtained for the variation of the density with temperature along this "reaction path":

$$(6)\quad d\rho \approx -\frac{mD^2}{2\,\bar{R}T_S^2} \cdot \rho_0 \cdot dT$$

where
m = average molecular weight
D = velocity of the detonation
R = gas constant
T_S = temperature behind shock-wave front
ρ_0 = initial density

For the variation in temperature in the initial stages of the chemical reaction, one obtains

$$(7)\quad dT \approx \frac{1}{\bar{C}_p} \Sigma\, d(x_i H_i)$$

$\bar{C}_p$ = average molar specific heat at constant pressure
x_i = mole fraction
H_i = molar enthalpy

Combination of Eqs. (5) to (7) gives:

$$(8)\quad \delta \approx -A \frac{1}{u} \cdot 2\pi\, \Sigma x_i \alpha_i \cdot \frac{D^2 \cdot \rho_0}{2\,RT_S^2 \cdot \bar{C}_p} \cdot \Sigma \frac{dx_i}{dt} \cdot H_i$$

Now a relationship must be established between dx_i/dt and the reaction mechanism. This relationship can be derived for the start of the $H_2 + O_2$ reaction, because its mechanism is well known from numerous earlier investigations [*].

The steps occurring at the beginning of the reaction (in the gas phase) consist of one initiation reaction, such as:

$$(0)\quad H_2 + O_2 \xrightarrow{k_0} 2\,OH \qquad E_a \approx 60 \text{ kcal/mole}$$
$$\longrightarrow HO_2 + H$$

two chain-branching reactions:

	E_a [kcal/mole]
(1) $H + O_2 \rightarrow OH + O$	≈ 18 -20
(2) $O + H_2 \rightarrow OH + H$	≈ 0 -10

and one ordinary chain step:

$$(3)\quad OH + H_2 \rightarrow H_2O + H \qquad E_a \approx 10 \text{ kcal/mole}$$

If it is assumed to a first approximation that at the beginning of the reaction the concentrations of the starting materials ($[H_2]$ and $[O_2]$) and the temperature behind the shock-wave front of the detonation are constant, then an approximate expression for the rate of formation of the individual particles H, OH, H_2O, *etc.* can be derived. The expression assumes the general form:

$$(9)\quad [N_i(t)] \approx \Sigma\, B_{li} e^{\alpha_l \cdot t} + D_{li}$$
where $l = 1$–3

The exponent α_l and the constants B_{li} and D_{li} are functions of the rate constants k_i pertaining to the individual steps and of the initial concentrations of hydrogen and oxygen, $[H_2]_0$, $[O_2]_0$. The explicit calculation of the constants B_{li} and D_{li} is lengthy and cannot be presented here. To a first approximation, it is found for times $t \leq t_i$, during which the concentration of the starting materials has decreased but little, that the term $\Sigma \frac{dx_i}{dt} \cdot H_i$ is proportional to $k_0 \cdot e^{\alpha_1 \cdot t}$ (k_0 = reaction rate of the initiation reaction), where

$$(10)\quad \alpha_1 \approx \frac{k_2 \cdot k_3 \cdot [H_2]_0}{2\,(k_2 + k_3)} \left(\sqrt{1 + \frac{8\,k_1\,[O_2]_0\,(k_2 + k_3)}{[H_2]_0^2 \cdot k_2 \cdot k_3}} - 1 \right)$$

Substituting $\frac{k_2 \cdot k_3}{k_2 + k_3}$ by k_c, one obtains:

$$(11)\quad \alpha_1 = \frac{k_c \cdot [H_2]_0}{2} \left(\sqrt{1 + \frac{8\,k_1}{k_c} \cdot \frac{[O_2]_0}{[H_2]_0}} - 1 \right)$$

Finally, one obtains approximately:

$$(12)\quad \delta \approx K \cdot k_0 \cdot e^{\alpha_1 t} \sim k_0\, e^{\alpha_1 t}$$

According to estimates, changes in the quantity K caused by variations of D, T_S, and ρ_0 are small compared to the changes induced in $k_0 e^{\alpha_1 t}$ by the experimental conditions. After the time t_i has elapsed, a certain angle of deflection δ_i is recorded, which is proportional to the attenuation of light intensity, as measured by the apparatus described on page 206. For evaluation, measurements at constant δ_i are compared [**]. Moreover, the absolute value of δ need not be known. It is only required that it is sufficiently small and thereby conforms as closely as possible to the assumed approximation of constancy of the starting materials and temperature.

[*] A whole series of data has resulted from investigations of the explosion limits of $H_2 + O_2$ in closed containers, and from a study of the elementary reactions $H + O_2$ and $O + H_2$. Cf., for example, *Jost* [3] and *Lewis* and *von Elbe* [6].

[**] Strict adhesion to this requirement is not very crucial, since (cf. page 200), after the onset of vigorous reaction following the induction period, t_i changes only to a negligible degree — even with large uncertainties in δ — as long as we consider only small values of δ (for example, at position C in Fig. 21).

With $k_0 \backsim \exp\left[-\frac{E_0}{RT_s}\right]$, one obtains from Eq. (12):

$$-\frac{E_0}{R \cdot T_s} + \alpha_1 \cdot t_i \approx \text{constant}$$

Evaluation of this equation, using the measured values of t_i, the initial concentrations of H_2 and O_2 behind the shock front, and the values of T_S calculated from the detonation velocity D, leads finally to a value for the sum of the energies of activation ($E_1 + E_c$) of 29 ± 2 kcal/mole. According to other measurements – comprehensively cited, for example, by *Jost* [2] and by *Lewis* and *von Elbe* [6] – the value of E_1 amounts to approximately 18 –20 kcal/mole. Thus, a value $E_c \approx 10 \pm 4$ kcal/mole is found.

These experiments do not permit a decision as to which reaction (2 or 3) this value is to be attached to. Supplementary experiments, which were carried out on detonations with admixture of nitrogen [81], seem to indicate, upon evaluation of the induction periods, that E_c should be ascribed to reaction (3). The magnitude of $E_c \approx E_3$ agrees very well with measurements of E_3 (of a different nature) carried out by *Avramenko* [73].

Another means of following the start of the reaction is provided by measuring of the increase of the OH concentration with time, for instance, during detonations in $H_2 + O_2$. The OH radical has a well-known band spectrum. The radical is critically involved in the mechanism of the $H_2 + O_2$ reaction and probably in the mechanism of many other combustion reactions with O_2 as well.

The band spectrum of OH has been thoroughly investigated. This involves a $^2\Pi \rightarrow {}^2\Sigma$ transition (absorption); the rotational lines of the (0–0) vibrational transition lie close to 3064 Å. The corresponding weaker lines, of, for example, the (1–0) transition, are found near 2800 Å. The oscillator strength f_c of the electronic transition $^2\Pi \rightarrow {}^2\Sigma$ has been determined by various authors [74, 75] from a careful measurement of individual absorption lines using high-resolution grating spectrometers. By these means, it is possible to infer the concentration of OH from measurements of the absorption of light by the OH group.

Just and *Wagner* [76] have carried riout expements of this kind in order to measure the absorption of OH behind the shock wave during a detonation. Applying the same assumptions as those described briefly on page 208 for the onset of the reaction, they determined the value of the rate constant of reaction (1) from measurements of the variation with time of the OH concentration in detonations of $H_2 + O_2$. They found

$k_1 \approx 3$ to 8×10^6 liters/mole/sec ($T = 1540$ °K)

Combining this with values determined previously at lower temperatures yielded an energy of activation of 18 ± 2 kcal/mole.

In the same paper, these authors estimated the effect on the initiation of the reaction produced by the diffusion of active particles (*e.g.*, H atoms) from the burnt gas toward the shock front. According to them, the role of diffusion in the onset of the chain-branching mechanism is of subordinate importance compared to that of the initiating reaction. The value of the activation energy of the initiating reaction E_0 can be deduced from determinations of the length of the induction period required for the first detectable appearance of the OH radical in the experimental setup. E_0 was found to lie between 50 and 80 kcal/mole.

From measurements by *Kovalsky* [78], *Semenov* [77] calculates a value for E_0 of about 45–50 kcal/mole. At any rate, the proposed initiation reaction $M + H_2 \rightarrow 2H + M$, with $E_0 \approx 103$ kcal/mole, is excluded, as far as the initiation of a detonation in $H_2 + O_2$ is concerned.

d) Measurements of the Reaction Time

A nonarbitrary definition of the reaction time is also impossible, since equilibrium in a chemical reaction is approached asymptotically with time. For purposes of comparison, however, an admittedly arbitrary, yet meaningfully defined reaction time can be very useful. In many instances, the measure of the reaction time is the lag of time between the passage of the shock front of the detonation and the attainment of a given fraction of the initial or final deflection of the measured quantity on the screen of the oscilloscope.

Measurement Techniques and Results

Kistiakowsky and *Kydd* [19] diluted mixtures capable of detonating (hydrogen + oxygen, methane + oxygen, carbon monoxide + oxygen with added hydrogen) with a heavy noble gas (krypton) and followed the variation of density in the reaction zone by means of absorption of soft X-rays by the krypton. The variation of density with time is shown in Figure 25.

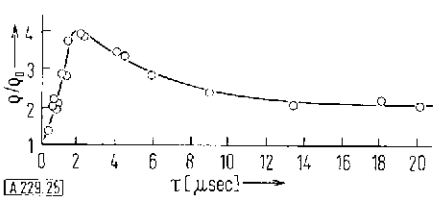


Fig. 25. Quantitative variation of the density in a detonation front with time as obtained in the experiments of *Kistiakowsky* et al. The increase of the density in the shock front and the relevant value of ρ_S could not be measured exactly because of the insufficient resolution ($\approx 10^{-6}$ sec) of the apparatus (after [19]).

Kistiakowsky et al. define τ_R as the time interval that elapses between the initial increase in density behind the shock front and the attainment of a value of the density given by

$$\frac{\rho_S + \rho_e}{2} \rightarrow \tau_{50} \quad \text{or} \quad \frac{\rho_S + \rho_e}{4} \rightarrow \tau_{75}$$

where ρ_e denotes the measured final density, which remains constant for a long period.

The above mixtures yield values of τ_{50} and τ_{75} of the order of microseconds. The fairly large amounts of noble gases (at least 30 %) that have to be added constitute a disadvantage. *Kistiakowsky* et al. assume that this had no substantial effect on the reaction mechanism.

Just, *Luig*, and *Wagner* [67, 76] applied a different technique. They measured the variation of the density gradient within the reaction zone with the schlieren technique, described on page 207. The reaction time was defined as the time interval from the moment the detonation shock wave passed the measuring site to

[73] *L. I. Avramenko* and *R. W. Lorenzo*, J. chem. Physik U.S.S.R. *24*, 207 (1950), Chem. Zbl. *1951*, 2263.

[74] *O. Oldenberg* and *F. Rieke*, J. chem. Physics *6*, 439 (1938).

[75] *R. Dwyer* and *O. Oldenberg*, J. chem. Physics *12*, 351 (1944).

[76] *Th. Just* and *H. Gg. Wagner*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *64*, 501 (1960).

[77] *N. Semenov*, Acta Physicochim. U.S.S.R. *20*, 291 (1945).

[78] *A. Kovalsky*, Physik. Z. Sowjetunion *1*, 595 (1932).

the moment at which 10 % of the maximum deflection caused by the reaction zone density gradient (at the end of the reaction zone, point d in Fig. 21) is reached. The values of τ_R measured in this fashion are of the same order of magnitude as those found by *Kistiakowsky*. Values of τ_R for various $H_2 + O_2$ mixtures at an initial pressure of the fresh gases of $P_0 = 100$ mm Hg are shown in Figure 26.

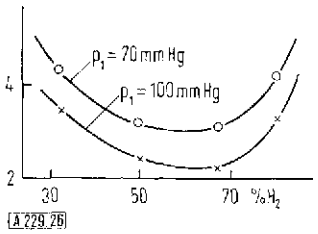


Fig. 26. Reaction times for various $H_2 + O_2$ mixtures measured by the schlieren method. The initial pressure of the fresh gas was 110 and 70 mm Hg. (after [67]). Ordinate: Reaction time [μsec].

The times given refer to the stationary-observer system. In accordance with the remarks on page 195, the motion of the gases behind the detonation front still has to be considered. An estimate for t_R to a first approximation is given by multiplying τ_R by an average value of the ratio of the density within the reaction zone. For a stoichiometric mixture of $H_2 + O_2$, this gives

$t_R \approx 6$ to 8 μsec; $P_0 = 110$ mm Hg.

It is impossible to evaluate with certainty the degree to which the chemical conversion has progressed at this time. Estimates obtained by following the changes in the OH concentration appear to indicate that at least 90 % of the value for equilibrium conversion should be assumed to have occurred prior to reaching this point.

The dependence of the reaction time on the pressure of the fresh gas can be represented sufficiently accurately by $\tau_R \sim 1/p$. This does not seem unreasonable since predominantly second-order reactions take place during the detonation of $H_2 + O_2$. This result must not be overestimated, however, because there are variations of temperature by a factor of about two (from 1500 to 3300 °K) and of density from approximately $\rho_0/\rho_1 \approx 5.4$ to $\rho_0/\rho_1 \approx 3$ within the reaction zone. The "reaction" time obtained represents an average value over the course of the reaction under widely varying conditions.

[79] *H. M. Mott-Smith*, Physic. Rev. *82*, 885 (1951).

[80] *C. S. Wang-Chang* and *G. E. Uhlenbeck*, Research Rep. CM-681 (1951), Univ. of Michigan.

[81] *Th. Just*, *D. McLean*, and *F. J. Luig*, Naturwissenschaften *48*, 476 (1961).

IV. Possibilities for Technological Applications of the Results and Methods

So far, shock waves have not been applied to industrial production of chemical compounds. Should a method using shock waves be worked out, it would seem expedient to apply pulsating shock waves, since a steady-state shock wave, which is obtainable by appropriate obstacles in a supersonic flow requires prior heating of the gas. The temperature of the quiescent gas before expansion into the supersonic nozzle must be of the same order as that produced within the shock wave. Therefore, such a process would involve extensive preliminary reactions, which render this technique useless. According to experiments by *Hertzberg*, *Glick*, and *Squire*, an apparatus generating periodic shock waves could possibly be utilized, for example, to produce acetylene in plants close to sources of natural gas. It would seem that the "driver gas" here could be derived from an appropriate detonation or explosion of natural gas with air (cf. Figure 1). Since the necessary calculations have not been worked out so far, this process will not be dealt with further here.

The behavior of flames at elevated temperatures and low pressures has gained considerable interest during recent years because of the development of jet engines and rocket motors. The methods and results of investigations with shock waves and detonations discussed above may be of some heuristic value in these fields. The same holds true for a number of problems such as ignition, reignition of motors at high altitudes, stabilization of flames behind flame-holders under widely varying conditions for feed gases, and many more. Essential knowledge of the dependence of the induction period (and presumably also the reaction time) on the composition of the mixtures, temperature, and pressure in these processes is still not very complete. However, it is to be hoped that the procedures discussed above will help to fill these gaps. Furthermore, employment of combustion behind shock waves for airplane engine systems of high Mach number ($M \geq 3$–4) has been under investigation for some time. Such engines have a relatively low thermodynamic efficiency, owing to losses in the shock front, but offer the advantage of extraordinary simplicity. This, too, requires extended knowledge of the behavior of fast combustion reactions behind shock waves and detonations.

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COMMUNICATIONS

A Cobalt Carbonyl/Carbon Disulfide Complex [1]

By Dr. L. Markó, Dr. G. Bor, and Dipl.-Chem. E. Klumpp

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$Co_2(CO)_8$ reacts with effervescence with excess CS_2. The reaction product consists for the most part of a precipitate which contains cobalt and sulfur and which is insoluble in ordinary solvents. Several derivatives of cobalt carbonyl, which are soluble in hexane, are formed as by-products. Chromatographic separation combined with infrared spectroscopic investigations indicate four soluble products. After evaporation of the CS_2 *in vacuo*, the residue is washed twice with a little hexane to remove readily soluble, unstable complexes and then digested with hexane at about 30 °C for three hours. After filtration, a black finely crystalline complex of composition $Co_4(CO)_{10}CS_2$ can be isolated by cooling the dark brown hexane solution stepwise to −70 °C (yield based on

cobalt 7.5 %). The compound is chromatographically pure and stable in air for a short period as the solid, but is quickly oxidized in solution. Under nitrogen, decomposition begins at about 105 °C, carbon monoxide being liberated; the carbon disulfide remains attached to the cobalt.

Infrared bands in the C–O vibration range (solution in hexane, relative intensities in brackets): 2107.0 (0.5); 2083.3 (4.2); 2063.8 (10.0); 2048.0 (5.6); 2042.0 (3.3); 2029.2 (1.7); and *ca.* 2022 cm^{-1} (shoulder, *ca.* 0.5). The remainder of the spectrum (in KBr discs): 1021 (m), 900 (w), 760 (m–w), 607 (m), 588 (m), 525 (s), 515 (s), 495 (s), and 464 cm^{-1} (m).

The absorption bands at 760, 900, and 1021 cm^{-1} indicate distortion of the linear arrangement and weakening of the C–S linkage as compared with free carbon disulfide. The position of the ν_1^{CO} band [2] characteristic for the completely symmetrical C–O vibration at 2107 cm^{-1} precludes the presence of dative bonds between the CS_2 group and the metal atoms. The structure of the novel complex may be similar to the "butterfly" arrangement discovered by *Dahl* [3], with the differences that there are no bridging CO groups in $Co_4(CO)_{10}CS_2$, and that the atoms of the CS_2 portion are linked by pure σ-bonds to the cobalt atoms.

Our results explain the inhibiting influence of carbon disulfide in oxosynthesis [4].

Received, January 11th, 1963 [Z 433/265 IE]

[1] Communication No. 4 on metal carbonyls containing sulfur. – Communication No. 3: *L. Markó, G. Bor, E. Klumpp, B. Markó,* and *G. Almásy,* Chem. Ber., in the press.

[2] *G. Bor,* 7th International Conference on Coordination Chemistry, Proceedings p. 8 (Stockholm, 1962); to be published shortly in Spectrochim. Acta.

[3] *L. F. Dahl* and *D. L. Smith,* J. Amer. chem. Soc. *84,* 2450 (1962).

[4] *V. Macho,* Chem. Zvesti (Bratislava) *15,* 181 (1961).

The Reaction of 4-Aminoantipyrine with 2,2-Di-(p-hydroxyphenyl)propane Derivatives

By Dr. F.T.Wallenberger [*]

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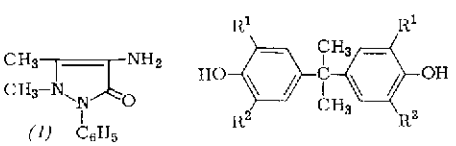
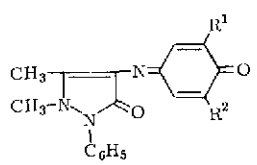
4-Aminoantipyrine *(1)* in basic medium containing catalytic amounts of potassium ferricyanide is one of the most sensitive analytical color reagents for phenols [1–4]. *Emerson* et al. [1] have shown that reaction occurs with all phenols



(1)

(2), R^1, R^2 = H
(3), R^1 = Cl, R^2 = H
(4), R^1, R^2 = Cl
(5), R^1, R^2 = CH_3



(7), R^1, R^2 = Cl
(8), R^1, R^2 = CH_3

possessing *para*-substituents such as -H, Cl, –COOH, $-SO_3H$, –OH, or $-OCH_3$, while *para*-substituents such as -aryl, -alkyl, $-NO_2$, –NO, $-COC_6H_5$, and –CHO are known to block the reaction [2–4]. *Gottlieb* and *Marsh* [2] observed that the diphenols *(2)* and *(3)* react quantitatively although the arylalkyl substituent *para* to the hydroxyl group ought to prevent substitution. They suggested reaction in unsubstituted *ortho*-positions here.

We have found that when *(1)* reacts with *(4)* or with 2,6-dichlorophenol *(6)*, identical red dyes are obtained. They have superimposable infrared and ultraviolet spectra (λ_{max} = 525 mμ). Equivalent amounts of *(4)* and *(6)* in acetone yielded the dye *(7)*, in nearly equal amounts as evidenced by the extinction at 525 mμ [*(4)* gives log ε_{max} = 4.58; *(6)* gives log ε_{max} = 4.61].

Compound *(5)* gave a brown dye, presumably *(8)*, when sprayed with *(1)* plus $K_3Fe(CN)_6$ on paper chromatograms; 4-t-butyl-2,6-dichlorophenol and 3,3',5,5'-tetrachloro-4,4'-dihydroxybiphenyl were unreactive. Evidently, 2,2-di-(*p*-hydroxyphenyl)propane derivatives react *para* to the phenolic hydroxyl with simultaneous elimination of the aryl alkyl substituent, contrary to *Emerson*'s rule and *Gottlieb* and *Marsh*'s hypothesis.

Compounds *(4)* and *(5)* both couple quantitatively with diazotized sulfanilic acid in slightly basic medium. Analogous coupling of either *(4)* or *(6)* gave the same dye, *viz.* 3,5-dichloro-4-hydroxyazobenzene-4'-sulfonic acid. If the mole ratio of diazotate: *(4)* is 1:1, part of the starting material remains unchanged, while a mole ratio of 1:0.5 gave only dye, showing that both phenolic fragments had reacted.

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[*] The technical assistance of *A. J. Prucino* is gratefully acknowledged.

[1] *E. Emerson, H. H. Beacham,* and *L. C. Beegle,* J. org. Chemistry *8,* 417 (1943).

[2] *S. Gottlieb* and *P. B. Marsh,* Ind. Engng. Chem., analyt. Edit. *18,* 16 (1946).

[3] *A. Rieche* and *L. Redinger,* Chem. Technik *10,* 41 (1958).

[4] *F. W. Ochynski,* Analyst *85,* 278 (1960).

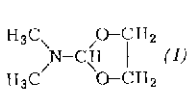
The Reaction of Carboxylic Acids and Phenols with Amide-Acetals

A New Method of Esterification and Etherification under Mildly Basic Conditions [1]

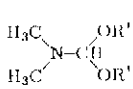
By Dr. H.Vorbrüggen [*]

Department of Chemistry, Stanford University, Stanford, California (U.S.A.)

Sterically unhindered ketones react with the cyclic "ethylene-acetal" of dimethylformamide *(1)* [2] on acid catalysis to form cyclic ethylene-ketals [1]. The carboxylic acid (acetic acid or trimethylacetic acid) used as catalyst forms the corresponding esters of ethylene glycol in a competing reaction [1]. This observation led to investigations of the reaction of amide-acetals with carboxylic acids and phenols. In polar solvents such as methylene chloride, ethylene dichloride, chloroform, or absolute ethanol, carboxylic acids and phenols react with a 3–4 fold molar excess of the diethylacetal of dimethylformamide *(2)* [2] to form the corresponding esters or ethers. On addition of the weakly basic reagent to a solution of the carboxylic acid, oily salts often separate but redissolve after a short reaction time. The dibenzylacetal of dimethylformamide *(3)*, which is obtained from the diethylacetal *(2)*, by transacetalization with benzyl alcohol, yields the corresponding benzyl esters or ethers in analogous reaction. Further reagents can be prepared with other primary or secondary alcohols [2].



(1)



(2), R' = C_2H_5
(3), R' = $CH_2C_6H_5$

The experiments compiled in Table 1 were performed with 0.5–20 mmoles of substance. On working on a larger scale, the yields of the volatile esters should be higher.

Amide-acetals react with acids and phenols similarly to diazoalkanes, but more slowly. The amide acetals are stable liquids and can be stored indefinitely on exclusion of water. They enable etherification or esterification reactions to be carried out under slightly basic conditions, but they condense easily with active methylene groups [2].

Table 1. Reactions of carboxylic acids and phenols with the diethylacetal *(2)* or dibenzylacetal *(3)* of dimethylformamide

Carboxylic acid or phenol	Acetal, solvent	Reaction temp. [°C]	Reaction time [h]	Product, m.p. [°C]	Yield [%]
Pyridine-3-carboxylic acid	*(2)* CH_2Cl_2	22	16	Ester	81
Adipic acid	*(2)* CH_2Cl_2	22	24	Diester	75
o-Hydroxybenzoic acid	*(2)* CH_2Cl_2	22	36	Ester	93
Fumaric acid	*(3)* CH_2Cl_2	22	35	Diester 62–63	81
β-Naphthoic acid	*(3)* $(CH_2Cl)_2$	84	3	Ester [3] 63–63,5	92
Phenol	*(3)* $(CH_2Cl)_2$	84	46	Ether	64
1,3,5-Trichlorophenol	*(2)* CH_2Cl_2	22	37	Ether 43–44	87

Experiments using these amide-acetals and the hitherto unknown thioacetals of dimethylformamide for the preparation of phosphate esters are in progress.

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[*] I wish to thank Professor *C. Djerassi* for his generous support, and Professor *W. S. Johnson* for his kind interest. Furthermore, thanks are due to Professor *A. Eschenmoser* for the exchange of information.

[1] Communication No. 2 on "The Reactions of Amide Acetals", Communication No. 1: *H. Vorbrüggen*, Steroids *1*, 45 (1963).

[2] *H. Meerwein, W. Florian, N. Schön*, and *G. Stopp*, Liebigs Ann. Chem. *641*, 1 (1961).

[3] This compound was hitherto unknown and has been characterized by analysis and infrared spectrum.

Hydrogenation of o-Nitrobenzonitrile to Anthranilamide

By Dr. H. Moll, Prof. Dr. H. Musso and cand. chem. H. Schröder

Laboratorium für Organische Chemie der Universität Lausanne (Switzerland) und Chemisches Institut der Universität Marburg/Lahn (Germany)

o-Nitrobenzonitrile *(1)* takes up 3 moles of hydrogen in 30 minutes when it is hydrogenated over palladium or platinum in methanol, *o*-aminobenzamide *(2)* being formed in 90 % yield [1]. If *(1)* is hydrogenated in the presence of heavy water (14.1 % ^{18}O) [2], no ^{18}O is incorporated into *(2)* (0.00 % ^{18}O); when *(2)* is subjected to the same hydrogenation conditions, it is again recovered unlabelled (0.05 % ^{18}O).

Labelled *(2)* with 13.3 % ^{18}O is obtained by hydrolysis of *o*-aminobenzonitrile *(3)* in heavy water. Catalytic hydrolysis of the nitrile by water produced in the hydrogenation reaction and adsorbed on the catalyst cannot occur, because within 30 minutes the labelled water which was added must equilibrate with the water on the catalyst to some extent. Moreover *(3)* is not hydrolysed in the presence of water under the conditions of the hydrogenation.

Hence the amide oxygen atom in *(2)* does not come from the water formed during hydrogenation, but apparently arises by attack of an oxygen atom of the nitro group in *(1)*.

Received, January 28th, 1963 [Z 441/271 IE]

[1] *H. Rupe* and *H. Vogler*, Helv. chim. Acta *8*, 832 (1925).

[2] The natural ^{18}O content is subtracted from the analytical figures. Analytical methods according to *H. Dahn, H. Moll*, and *R. Menasse*, Helv. chim. Acta *42*, 1225 (1959).

Esterification of Carboxylic Acids with Aminoacetals

By H. Brechbühler, H. Büchi, E. Hatz, Dr. J. Schreiber, and Prof. Dr. A. Eschenmoser

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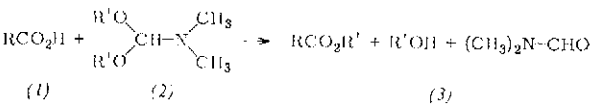
In connection with studies in the peptide series, we have established that dialkylacetals of *N,N*-dimethylformamide [1] represent preparatively valuable reagents for esterifying carboxylic acids [2].



(1) *(2)* *(3)*

Benzoic acid (0.4 M) reacts [2] with two equivalents of the diethylacetal of *N,N* dimethylformamide to give ethyl benzoate under the following conditions: in methylene chloride for 5 hr at 40 °C; in benzene for 1 hr at 80 °C; in acetonitrile for 36 hr at room temperature. In all cases the yields are greater than 90 % [3].

Esterification of benzoic acid with the acetal made from dimethylformamide and (+)-*S*-butan-2-ol proceeds with almost complete inversion, either in benzene at 80 °C or in acetonitrile at room temperature. This confirms the view that the reaction involves alkylation of the carboxylate oxygen. In accordance with the S_N2-character of the reaction, benzoic acid cannot be esterified by the acetal made from *N,N*-dimethylformamide and neopentyl alcohol. In addition, reaction of the diethylacetal of *N,N*-dimethylformamide with 2,4,6-trimethylbenzoic acid, which is sterically hindered for $A_{Ac}2$-esterification, yielded the ethyl ester almost as rapidly as with benzoic acid.

Table 1. Esterification of amino acids and dipeptide derivatives *(1)* with acetals formed from dimethylformamide and benzyl or *p*-dodecylbenzyl alcohol [*(4)* and *(5)* respectively]

(1) [mole/l]	Acetal [equiv.]	Solvent, Temp., Time [hr]	Ester M.p. [°C]	Ester $[\alpha]_D$ in $CHCl_3$	Yield [b] [%]
N-DOBC-L-Val [a] [0.014]	*(4)* [1.5]	Benzene, 80 °C, 1.5	63	0°	97
N(α)-DOBC-L-Try [0.015]	*(4)* [1.6]	Benzene, 80 °C, 1.5	90	+12.0°	78
N-DOBC-Gly-L-Leo [0.016]	*(4)* [1.6]	Benzene, 80 °C, 1	57	−6.2°	73
N-DOBC-L-Phe [0.067]	*(5)* [1.3]	CH_2Cl_2, 20 °C, 18	93	+5.2°	84
N(α)-DOBC-L-Try [0.086]	*(5)* [1.3]	CH_2Cl_2, 20 °C, 50	109	+6.2°	68
N-DOBC-L-Phe-L-Ala [0.051]	*(5)* [1.3]	CH_2Cl_2 20 °C, 120	109	+2.4°	75

[a] DOBC = $CH_3-(CH_2)_9-O-C_6H_4-CH_2-O-CO-$. Preparation of these derivatives: *H. Peter, H. Büchi*, and *J. Loeffler*, unpublished.

[b] Crystalline, analytically pure material shown to be homogeneous by thin-layer chromatography.

Our findings regarding the esterification of amino acids and dipeptide derivatives by acetals formed from *N,N*-dimethylformamide and either benzyl or *p*-dodecylbenzyl alcohol [*(4)* and *(5)*, respectively] are reproduced in Table 1. The benzyl ester of L-valine hydrochloride was isolated in 83 % yield after removal of the *N*-protecting group from the benzyl ester of *N*-DOBC-L-valine with trifluoroacetic acid [4], and corresponds in melting point (138 °C) and in specific rotation (+9.7° in pyridine) with data reported in the literature [5].

The acetals of *N,N*-dimethylformamide were obtained from *N,N*-dimethylformamide by transacetalization [1] using the diethyl- [1] or dimethylacetal [6]. This method failed in the case of *p*-nitrobenzyl alcohol.

Received, February 4th, 1963 [Z 450/283 IE]

[1] *H. Meerwein, W. Florian, N. Schön*, and *G. Stopp*, Liebigs Ann. Chem. *641*, 1 (1961).

[2] *W. Häusermann*, diploma thesis, Eidgenössische Technische Hochschule, Zürich (Switzerland), 1962.

[3] Estimated by recovery of unesterified benzoic acid.

[4] *F. Weygand* and *K. Hunger*, Chem. Ber. *95*, 1 (1962).

[5] *J. Shields, W. H. McGregor*, and *F. Carpenter*, J. org. Chemistry *26*, 1491 (1961).

[6] *H. Bredereck, F. Effenberger*, and *G. Simchen*, Angew. Chem. *73*, 493 (1961).

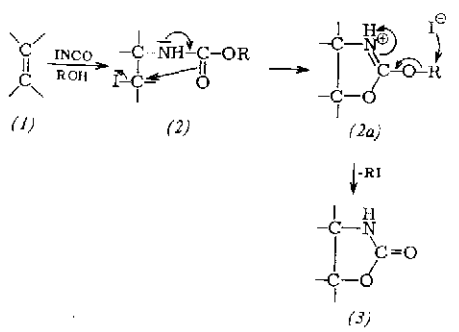
Formation of 2-Oxazolidones from β-Iodourethanes

A Stereospecific Synthesis of cis-β-Amino-Alcohols [1]

By Dr. C. Heathcock [2] and Prof. Dr. A. Hassner [3]

Department of Chemistry, University of Colorado, Boulder, Colorado (U.S.A.)

Iodine isocyanate adds to olefins to yield β-iodo-isocyanates which react with alcohols to give β-iodo-urethanes [1,4]. When the olefin used is cyclic, a *trans*-adduct *(2)* is obtained [1,5], which can be converted into a 2-oxazolidone *(3)*.



(1) *(2)* *(2a)* *(3)*

The results obtained so far are given in Table 1. The 2-oxazolidones were produced by pyrolysis of the corresponding β-iodo-urethanes, either by heating alone at 100–190 °C, or in a refluxing solvent. That the reaction involves inversion at the carbon bearing iodine is shown by the fact that *cis*-cyclohexano[*b*]-2-oxazolidone [6] is obtained on pyrolysis of methyl-*trans*-2-iodo-cyclohexane carbamate. Alkyl iodides have been isolated as by-products in almost quantitative yield in these reactions. Hydrolysis of the 2-oxazolidones leads to *cis*-β-amino-alcohols. For example Cholestano[3β, 2β-*b*]-2-oxazolidone was hydrolysed by methanolic potassium hydroxide to give a 93 % yield of 2β-aminocholestan-3β-ol, m.p. 166 °C; *N,O*-diacetyl derivative, m.p. 194 °C.

Table 1. 2-Oxazolidones prepared so far

Olefin	2-Oxazolidone	Yield [*] [%]	m.p. [°C]
2-Cholestene	Cholestano[3β, 2β-*b*]-	53	227
1,2-Dihydronaphthalene	*cis*-Tetralino[2,1-*b*]-	35	141
Indene	*cis*-Indano[2,1-*b*]-	61	160
Styrene	4-Phenyl-	81	136 [7]
Cyclohexene	*cis*-Cyclohexano[*b*]-	41	55 [6]

[*] Based on olefin; intermediate β-iodo-urethanes were isolated and purified.

The β-iodo-urethanes *(2)* can be hydrolysed with base to give the corresponding ethylene-imines; the imine ring can then be opened with acid to give *trans*-β-amino-alcohols [1]. These reactions make available a stereospecific route to *cis*- as well as to *trans*-β-aminoalcohols from olefins.

Received, February 5th, 1963 [Z 452/273 IE]

[1] Communication No. 2 on "The Chemistry of Urethanes". Communication No. 1: *A. Hassner* and *C. Heathcock*, Tetrahedron Letters, in the press.

[2] National Science Foundation Predoctoral Fellow.

[3] Financial assistance by the U. S. National Institutes of Health, Grant CY-4474 is gratefully acknowledged.

[4] *L. Birckenbach* and *M. Lindhard*, Ber. dtsch. chem. Ges. *64*, 1076 (1931); *G. Drefahl* and *K. Ponsold*, Chem. Ber. *93*, 519 (1960).

[5] *R. Wittekind, J. Rosenau*, and *G. Poos*, J. org. Chemistry *26*, 444 (1951).

[6] *M. Mousseron* et al., Bull. soc. chim. France *1953*, 737.

[7] *M. S. Newman* and *A. Kulner*, J. Amer. chem. Soc. *73*, 4199 (1951).

Acylation of Enamines with Lactimsulfonic Esters [1]

By Prof. Dr. S. Hünig, Dr. W. Lücke, Dr. V. Meuer [2], and cand. chem. W. Grässmann

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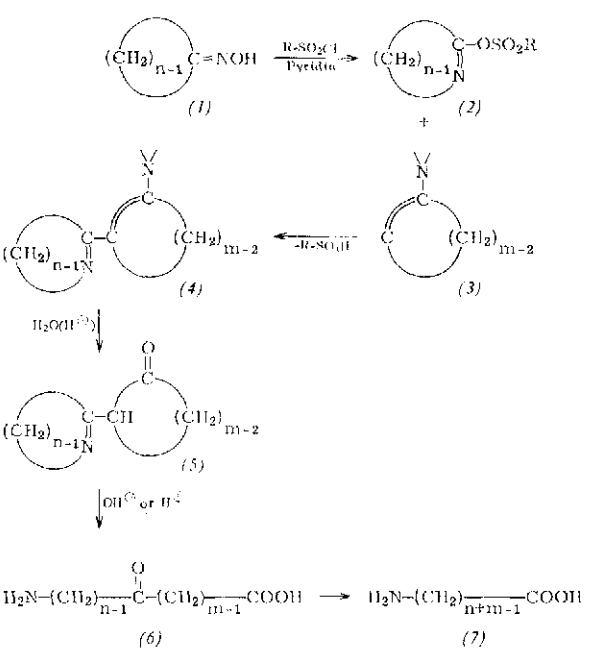
The smooth acylation of enamines with carbonyl chlorides [3] can also be applied to iminosulfonic esters, which are formed for example on Beckmann rearrangement of cyclic ketoximes *(1)* and which condense with enamines to give *(4)*.



(1) *(2)* *(4)* *(3)* *(5)* *(6)* *(7)*

Compound *(4)* is isolatable and is split by dilute acid to give the equally stable iminoketone *(5)* [4], which, when the ring sizes are suitable, are split by alkali or strong acids into ω-amino-keto-acids *(6)*. Long chain ω-aminocarboxylic acids are obtained finally by reduction (examples, see Table 1).

Table 1. Reaction sequence *(2)* + *(3)* → *(4)* $\xrightarrow{H^{\oplus}}$ *(5)* $\xrightarrow{OH^{\ominus}}$ *(6)*.

(2)	*(3)*	Product	Yield [%]	B.p. [°C/mm Hg or m.p. [°C]
C_6	C_8	*(4)*	57	144–150/0.01
C_6	C_{13}	*(4)*	54	133–155/0.007
C_6	C_{10}	*(5)*	43	150–155/0.03
C_7	C_6	*(5)*	57	120–125/0.2
C_6	C_6	*(6)*	94 [a]	136–137 [b]
C_8	C_6	*(6)*	74 [a]	168–169

[a] Calculated for the step *(5)* → *(6)*.
[b] Hydrochloride.

12-Amino-7-ketododecanoic acid *(6)* can be reduced with hydrazine to give 12-aminododecanoic acid (m.p. 179 to 181 °C.) 75 % yield.

Received, February 7th, 1963 [Z 445/275 IE]

[1] Syntheses with Enamines X; Part IX: *S. Hünig* and *W. Eckardt*, Chem. Ber. *95*, 2493 (1962).

[2] *V. Meurer*, Ph. D. thesis, Universität Würzburg, 1962.

[3] Cf. *M. Coenen*, Angew. Chem. *61*, 11 (1949); *G. Stork*, *R. Terrell*, and *J. Szumszkovicz*, J. Amer. chem. Soc. *76*, 2029 (1954); *S. Hünig*, *E. Benzing*, and *E. Lücke*, Chem. Ber. *96*, 2833 (1957) and subsequent publications.

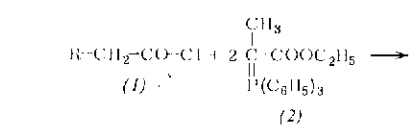
[4] Tautomeric forms are possible here.

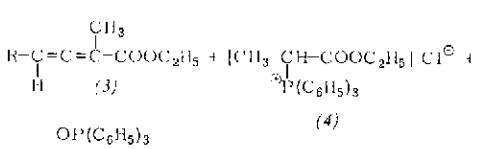
New Synthesis of Allenecarboxylic Esters

By Priv.-Doz. Dr. H. J. Bestmann
and Dipl.-Chem. H. Hartung

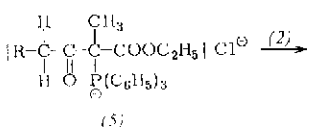
Institut für Organische Chemie
der Technischen Hochschule, München (Germany)

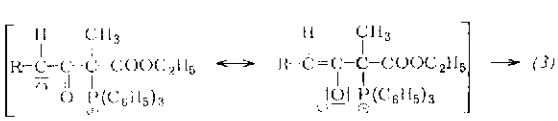
α-Ethoxycarbonylethylidene triphenylphosphorane *(2)* reacts with acid chlorides *(1)* to give allenecarboxylic esters *(3)*, triphenyl-(α-ethoxycarbonyl)ethyl phosphonium chloride *(4)*, and triphenylphosphine oxide:





As a first step, an acylated phosphonium salt is formed from *(1)* and *(2)*:





Compound *(2)* then abstracts a proton from the γ-position to the phosphorus atom. The mesomeric carbanion formed rearranges into *(3)*. The yields are quoted in Table 1.

Table 1. Reaction *(1)* + *(2)* → $RCH{=}C{=}C(CH_3){-}COOC_2H_5$ *(3)*

Acid chloride *(1)* of:	R	B.p. [°C/mm] of *(3)*	Yield [%]
acetic acid	H	52/11	59
butyric acid	C_2H_5	70/11	55
n-caproic acid	C_4H_9	97/11	66
oenanthic acid	C_5H_{11}	109/11	80
dihydrocinnamic acid	$C_6H_5{-}CH_2$	114/1	51

The infrared spectra of all the esters *(3)* listed contain a pronounced allene band at 1950 cm^{-1}. The derivative obtained from dihydrocinnamic acid polymerizes slightly on distillation. Starting from phenylacetic acid, an allenecarboxylic ester is obtained with R = C_6H_5 which is stable only in solution and which polymerizes completely on evaporation.

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Decomposition of Diimine

By Prof. Dr. S. Hünig, Dr. H. R. Müller [1],
and Dipl.-Chem. W. Thier [2]

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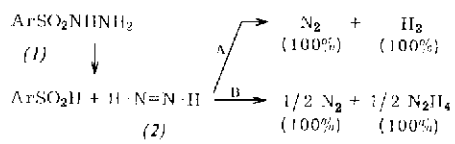
Chemisches Institut der Universität Würzburg (Germany)

According to *Raschig* [3], diimine *(2)* [4] is formed on thermolysis of arylsulfonylhydrazides *(1)* in strong alkali but then breaks down into its constituent elements.



We have found that the fission of *(1)* in boiling methoxyethanol is dependent on the excess of alkali (Table 1). It was only when the medium was strongly basic that the reaction

Table 1. Yields of N_2, H_2, and N_2H_4 on fission of 5.00 mmoles of benzenesulfonylhydrazide in 50 ml of methoxyethanol with varying concentrations of KOH (temperature *ca.* 125 °C)

KOH [mole/l]	% N_2	% H_2	% N_2H_4	Route A:B
2.50	98 ± 2	97 ± 2	2 ± 2	48.5:1
0.63	91	83	16	5.2:1
0.32	77	54	46	1.3:1
0.17	65	29	73	0.4:1

proceeded according to *Raschig*. With decreasing concentration of alkali, the total volume of gas decreased with proportional lessening of the formation of hydrogen. At the same time, the corresponding amount of hydrazine was formed. This is due to the increasing importance of route B, since added olefins are hydrogenated to a proportionate degree.

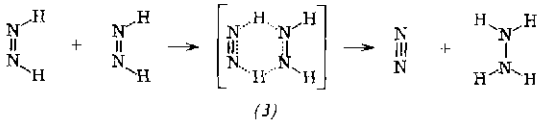
Table 2. Reaction of 5.48 mmoles of styrene and 5.00 mmoles of benzenesulfonylhydrazide in 16.5 ml of methoxyethanol with varying concentrations of KOH (temperature *ca.* 126 °C)

KOH [mole/l]	2.00	1.00	0.25	0.125
Hydrogenation yield (ethylbenzene)	72 ± 2	80	91	100

The percentages of N_2 and N_2H_4 in Table 1 therefore give a direct indication of the proportion of the rates with which diimide reacts further along routes A and B, respectively. This makes it probable that route A proceeds as follows:

$$HN{=}NH + OH^{\ominus} \rightleftarrows H_2O + HN{=}N^{\ominus}$$
$$HN{=}N^{\ominus} \rightarrow N_2 + H^{\ominus};\ H^{\ominus} + HB \rightleftarrows H_2 + B^{\ominus}$$

whereas the newly discovered disproportionation according to route B can be regarded as a hydrogenation of an azo double bond [4]. The structure *(3)* can be considered as a transition state, especially since diimide produced from benzenesulfonylhydrazide hydrogenates added tolane stereospecifically to give *cis*-stilbene in at least 95 % yield, according to infrared analysis.



(3)

The consequences of this auto-hydrogenation are currently being investigated.

Received, February 13th, 1963 [Z 449/279 IE]

[1] *S. Hünig* and *H. R. Müller*, Ph. D. thesis, Universität Würzburg 1962.

[2] *S. Hünig* and *W. Thier*, Diplom thesis, Universität Würzburg 1963.

[3] *S. Hünig* et al., Tetrahedron Letters *11*, 353 (1961); *E. J. Corey* et al., *ibid. 11*, 347 (1961); *E. E. van Tamelen* et al., J. Amer. chem. Soc. *83*, 3725 (1961).

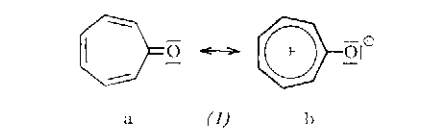
[4] *F. Raschig*, Angew. Chem. *23*, 972 (1910).

New Heptafulvene Derivatives

By Prof. Dr. K. Hafner, Dr. H. W. Riedel, and Dipl.-Chem. M. Danielisz

Chemisches Institut der Universität Marburg (Germany)

We have found that the reactivity of the carbonyl group in cycloheptatrienone *(1)* can be increased by *O*-alkylation. With triethyloxonium fluoroborate [1], *(1)* gives a quantitative yield of ethoxytropylium fluoroborate *(2)* (m.p. 40 °C), which reacts smoothly with malonic dinitrile in the presence of bases to form thermostable orange 8,8-dicyano-, heptafulvene *(3)* (m.p. 200 °C; λ_{max} = 252 (log ε = 3.98). 368 (4.26), 374 (4.27), and 381 (4.27) mμ in n-hexane) [2]. Other reactive methylene compounds also react thus with compound *(2)* to yield heptafulvene derivatives.

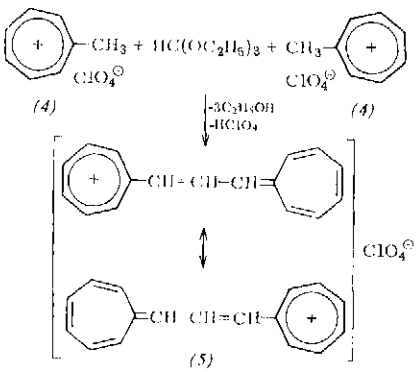


a *(1)* b

(2) *(3)*

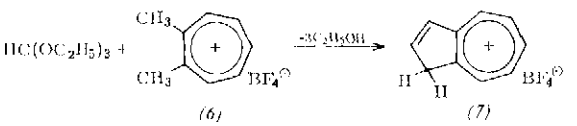
Heptafulvene derivatives also result from condensation of methylated tropylium salts with orthoesters of carboxylic acids or their vinylogs in acetic anhydride [3]. Methyltropylium perchlorate *(4)* and triethyl orthoformate yield the deep blue [3-(cycloheptatrienylidene)allyl]tropylium perchlorate *(5)* (decomp. > 200 °C; λ_{max} = 604 mμ; log ε = 4.1 in acetonitrile), a non-benzenoid isomer of the diarylpolymethine-carbonium salts [4].

Analogous colored salts are formed from compound *(4)* and azulene-1-aldehyde (deep blue crystals, decomp. > 150 °C; λ_{max} = 632 mμ; log ε = 3.7 in acetonitrile) and *p*-dimethylaminobenzaldehyde (deep blue crystals, decomp. > 150 °C; λ_{max} = 657 mμ; log ε = 3.76 in acetonitrile).



(4) *(4)* *(5)*

1,2-Dimethyltropylium fluoroborate *(6)* reacts with ethyl orthoformate in acetic anhydride to give the known azulenium fluoroborate *(7)* [5].



(6) *(7)*

Received, February 13th, 1963 [Z 448/278 IE]

[1] Cf. *H. Meerwein* et al., Liebigs Ann. Chem. *641*, 1 (1961).

[2] Compound *(3)* has also been prepared by another route by *T. Nozoe* et al., see *J. W. Cook*, Progr. org. Chemistry *5*, 159 (1961).

[3] *K. Hafner* et al., Liebigs Ann. Chem. *624*, 37 (1959); *650*, 80 (1961); Angew. Chem. *71*, 378 (1959).

[4] *K. Hafner* and *H. Pelster*, Angew. Chem. *73*, 342 (1961).

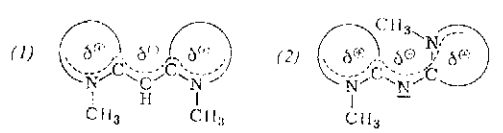
[5] *K. Hafner* et al., Liebigs Ann. Chem. *650*, 62 (1961).

Investigations of Cyanine Dyes by P.M.R. Spectroscopy

By Dr. H. J. Friedrich

Chemisches Institut der Universität Würzburg (Germany)

Cyanine dyestuffs of type *(1)* can occur in geometrically isomeric forms and for steric reasons mostly exist in one fixed configuration under normal conditions [1]. Proton resonance of the $\delta^{\oplus}\rangle N-CH_3$ group is particularly suitable for determining this configuration and for investigating its geometric isomerism [2].



(1) *(2)*

Symmetrical methinecyanines with a planar structure and an all-*trans*-configuration [1] *e.g.* *N,N'*-dimethylpseudoisocyanine or *N,N'*-dimethyl-dibenzoxazolo-monomethinecyanine, give a single $\delta^{\oplus}\rangle N-CH_3$ proton-resonance signal. Two different $\delta^{\oplus}\rangle N-CH_3$ resonance signals are observed with formally symmetrical, but for steric reasons non-planar derivatives, *e.g. meso*-substituted *N,N'*-dimethyldibenzthiazolomonomethinecyanines. Similarly, formally symmetrical planar cyanines with a mono-*cis*-configuration [1], *e.g.* *N,N'*-dimethyldipyridomonomethinecyanine, give two different $\delta^{\oplus}\rangle N-CH_3$ signals.

The P.M.R. spectra show that all the azacyanines so far investigated exist (for an as yet unknown reason) in the mono-*cis*-form *(2)*, *e.g.* the *N,N'*-dimethylmono-azacyanines containing pyridine, quinoline, and benzthiazole rings. This surprising result is supported even further by ultraviolet and infrared spectroscopic findings.

These results supply information on the fine structure of the cyanines and contribute to the theoretical interpretation of these dyes. Our investigations are therefore continued on a broad basis.

Received, February 15th, 1963 [Z 454/292 IE]

[1] *G. Scheibe, H. J. Friedrich,* and *G. Hohlneicher,* Angew. Chem. *73*, 383 (1961).

[2] The investigations were carried out with a Varian A 60 Mode NMR-Spectrometer.

Preparation of 1-Hydroxypropane-2-sulfonic Acid

By Dr. Heinz Schmitz, Dr. H. Grosspietsch, Dr. H. Kaltenhäuser, and Dr. H. Wendt

Farbwerke Hoechst AG. vormals Meister Lucius & Brüning, Frankfurt/Main-Höchst (Germany)

1-Hydroxypropane-2-sulfonic acid is said to have been prepared by *Raschig* and *Prahl* [1] by treating chloropropylene glycol acetate with K_2SO_3 (synthesis I) and by *Manecke* [2] by hydrolysis of an anhydride of the acid made by treating sulfuryl chloride with n-propanol and dehydrochlorinating the propyl chlorosulfonate obtained (synthesis II). As rearrangements may possibly occur in these syntheses, we have prepared 1-hydroxypropane-2-sulfonic acid by reduction of α-sulphonylpropionic acid with $LiAlH_4$ in dioxan (synthesis III).

$$H_3C{-}\underset{\displaystyle SO_3H}{\underset{|}{CH}}{-}COOH \xrightarrow[\text{dioxan}]{LiAlH_4} H_3C{-}\underset{\displaystyle SO_3H}{\underset{|}{CH}}{-}CH_2OH$$

The infrared spectrum of the barium salt of this acid was different from those of the barium hydroxypropanesulfonates made by syntheses I and II, which corresponded. The hydroxypropanesulfonic acid made by the other authors must therefore be either 2-hydroxypropane-1-sulfonic acid or 1-hydroxypropane-3-sulfonic acid. The latter is obtainable by hydrolysis of 1,3-propanesultone; the infrared spectrum of its barium salt differs from the spectra of the barium salts obtained by syntheses I, II, and III. 2-Hydroxypropane-1-sulfonic acid was made by reduction of acetonesulfonic acid (synthesis IV); its barium salt had the same infrared spectrum as that of the barium salts from syntheses I and II.

It can also be shown by comparison of the melting points of the phenylhydrazonium salts and of the *N*-methylaminopropanesulfonic acids (obtained by reaction with methylamine) that the hydroxypropanesulfonic acids described both by *Raschig* and *Prahl* and by *Manecke* are in fact 2-hydroxypropane-1-sulfonic acid.

Method of synthesis	Phenylhydrazonium salt m.p. [°C]; mixed m.p. [°C]	*N*-Methylaminopropanesulfonic acid m.p. [°C]; mixed m.p. [°C]
II	136 } 114	193.5
III	125.5 }	–
IV	135	194
II + IV	135	193.5

Willems [3] also designated a substance he obtained from 2-bromopropanol and Na_2SO_3 as 1-hydroxypropane-2-sulfonic acid, as it proved to be identical with the acid described by *Manecke*. It appears from our work that *Willems* too obtained 2-hydroxypropane-1-sulfonic acid.

Received, February 21st, 1963 [Z 451/280 IE]

[1] *F. Raschig* and *W. Prahl,* Ber. dtsch. chem. Ges. *61*, 185 (1928).

[2] *G. Manecke,* Chem. Ber. *85*, 160 (1952).

[3] *J. Willems,* Bull. Soc. chim. Belg. *64*, 409 (1955).

Detection of the Phenylsulfur Radical [1]

By Dozent Dr. Ulrich Schmidt and Dipl.-Chem. Asmus Müller

Chemisches Laboratorium der Universität Freiburg/Breisgau (Germany)

Ionic radicals of doubly-bonded sulfur ($R{-}\overset{\oplus}{S}\overset{\bullet}{}{-}R$) were detected by us in oxidized solutions in sulfuric acid of di-*p*-methoxyphenyl sulfide, p-di(arylthio)benzenes, and tetraphenylthiophenes [1]. Free radicals of singly-bonded sulfur ($R{-}S\bullet$) have been sought repeatedly, but were not found hitherto [2]. However, the existence of the phenylsulfur radical ($Ph{-}S\bullet$) has now been demonstrated by us.

On irradiating diphenyl sulfide vapor with short-wave ultraviolet light at 1 mm. Hg pressure and high carrier-gas (N_2) speeds, phenylsulfur radicals were detected as thiophenol by dehydrogenation of injected cumene 10 cm from the irradiated zone.

Irradiation of diphenyl sulfide vapor without carrier-gas at 0.1 mm Hg pressure resulted in the formation of a red coating of $Ph{-}S\bullet$ a few cm away on a finger cooled with liquid nitrogen. This was stable for some hours *in vacuo* at −200 °C, but disappeared within a few minutes at −100 °C. Thiophenol was formed by disproportionation or dehydrogenation of diphenyldisulfide.

Measurement of the electron spin resonance spectrum at −200 °C showed a strong signal with a typically anisotropic g factor. The g tensor is almost axisymmetrical with limiting values $g_\perp = 2.006$ and $g_\parallel = 2.012$ as far as can be determined from the powder spectra. This indicates that the unpaired electron is associated mainly with the sulfur, since such a large degree of g anisotropy can only be explained by an electron which is strongly localized.

Received, February 25th, 1963 [Z 453/281 IE]

[1] Communication No. 2 on Organosulfur Radicals; Communication No. 1: Angew. Chem. *72*, 708 (1960).

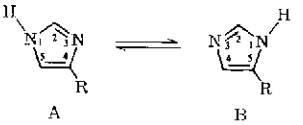
[2] For literature references, see Communication No. 3, Liebigs Ann. Chem., in the press.

Proton-Resonance Investigations of "4 (or 5)-Substituted Imidazoles"

By Prof. Dr. H. A. Staab and Dr. A. Mannschreck

Organisch-chemisches Institut der Universität Heidelberg (Germany)

Tautomeric forms A and B of 4 (or 5)-substituted imidazoles cannot be isolated [1]. It has also not been possible to determine whether these compounds exist as either structure A or structure B.

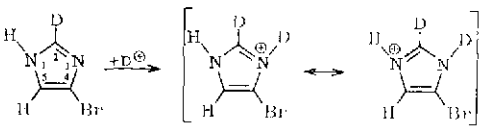


A B

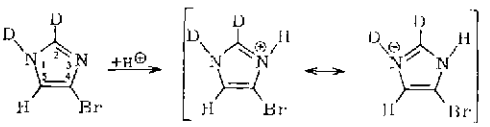
Concepts, such as the hypothesis of a special "mesohydric tautomerism" [2], or the postulate [3] based on spectroscopic results that, in both the crystalline state and non-polar solvents, imidazoles exist as ion-pairs made up of imidazole anions and imidazole cations led to the assumption that it is impossible to differentiate between 4- and 5-substituted imidazoles [3,4]. Our proton-resonance experiments show that such postulates do not apply to the 4(or 5)-substituted imidazoles investigated in the present work. They demonstrate that these compounds exist predominantly in one definite form, for which distinction can be made between 4- and 5-substitution on the basis of the respective spin-spin coupling constants.

If 4(or 5)-bromoimidazole *(1)* which is deuterated in the 2-position to simplify its proton resonance spectrum, is dissolved in conc. D_2SO_4, a doublet with J = 2.7 cps is observed for the 4 (or 5) resonance of the imidazole cation as a result of coupling with the *N*-1 proton [5]; this doublet is converted into a singlet by exchange of the *N*-1 proton for deuterium (half-life: *ca.* 30 min.; *ca.* 35 °C; 0.3 mole/l). On the other hand, in conc. H_2SO_4, [1,2-^{2}H]-4(or 5)-bromoimidazole *(3)* shows a different doublet with J = 1.9 cps; this is transformed by deuterium-hydrogen exchange into a pair of doublets already known for the [2-^{2}H]-4(or 5)-bromoimidazolium-cation in H_2SO_4 [5].

Thus, [2-^{2}H]-4(or 5)-bromoimidazole *(1)* in D_2SO_4 and the corresponding *N*-1-deuterated compound *(3)* in H_2SO_4 give two different isomeric cations, *(2)* and *(4)*. The assignment of these structures is based on the assumption, valid for such five-membered ring systems [6], that the greater coupling constant (J = 2.7 cps) corresponds to the cation *(2)* in which the interacting protons are adjacent. As a result, the imidazoles *(1)* and *(3)* are protonated as the 4-substituted isomers.



(1) *(2)*: Doublet J_{15} = 2.7 cps



(3) *(4)*: Doublet J_{35} = 1.9 cps

Analogous results were obtained with 2-methyl-4(or 5)-bromoimidazole (J_{15} = 2.6 cps; J_{35} = 2.0 cps; half-life of H/D exchange: *ca.* 200 min.). Investigations on histidine and histamine are in progress; the results are more complex here owing to additional coupling of the 4(or 5)-proton with the methylene group of the side-chain.

Received, March 5th, 1963 [Z 460/289 IE]

[1] Literature survey: *K. Hofmann:* Imidazole and its Derivatives. Interscience Publishers, New York 1953; *E. S. Schipper* and *A. R. Day:* Imidazoles and Condensed Imidazoles, in *R. C. Elderfield:* Heterocyclic Compounds, Wiley, New York 1957, vol. 5, p. 194.

[2] See, for example, *L. Hunter*, J. chem. Soc. (London) *1945*, 806.

[3] *W. Otting*, Chem. Ber. *89*, 2887 (1956).

[4] *E. H. Rodd:* Chemistry of Carbon Compounds, Elsevier, Amsterdam 1957, vol. IVA, p. 286; see also *H. Bredereck, R. Gompper*, and *F. Reich*, Chem. Ber. *93*, 723 (1960).

[5] A detailed report on the proton resonance of imidazoles and imidazolium cations is given by *A. Mannschreck, W. Seitz*, and *H. A. Staab*, Ber. Bunsenges. physik. Chem., in the press; see also *H. A. Staab* and *A. Mannschreck*, Tetrahedron Letters *1962*, 913.

[6] *B. Dischler* and *G. Englert*, Z. Naturforsch. *16a*, 1180 (1961); *S. Gronowitz, A. B. Hörnfeldt, B. Gestblom*, and *R. A. Hoffmann*, Arkiv Kemi *18*, 133, 151 (1961); *R. J. Abraham* and *H. J. Bernstein*, Canad. J. Chem. *39*, 905 (1961); *H. A. Staab* and *A. Mannschreck*, to be published in Chem. Ber.

Synthesis of Amidrazones from Nitriles and Sodium Hydrazide

By Dr. Th. Kauffmann, Dipl.-Chem. S. Spaude, and Dipl.-Chem. Dieter Wolf

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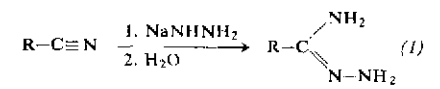
Amidrazones *(1)* have so far been accessible only with difficulty [1]. This is reflected in the fact that acetamidrazone is the only amidrazone of the fatty acid series that has been described [2].

We have now found that successive action of sodium hydrazide [3] (at 0–20 °C under nitrogen) and water on aliphatic and aromatic nitriles affords amidrazones conveniently in good yields.



(1)

The following amidrazones were prepared: (m.p. in parentheses, except for known compounds): acetamidrazone (as its hydrochloride; 63 %); caprinamidrazone (m.p. 82 °C; 87 %); lauramidrazone (m.p. 86 °C; 85 %); myristamidrazone (m.p. 91 °C; 100 %); heptadecanecarboxamidrazone (m.p. 95 °C; 93 %); stearamidrazone (m.p. 96 °C; 74 %); phenylacetamidrazone (oil; m.p. of picrate 151–153 °C; 78 %); benzamidrazone (99 %); salicylamidrazone [4] (m.p. 173 °C; 100 %); α-naphthamidrazone (m.p. 121–123 °C; 57 %); and β-naphthamidrazone (88 %).

Corresponding reactions employing dinitriles and polynitriles and syntheses of heterocyclic compounds employing the above amidrazones are currently being investigated.

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[1] The most successful method of preparation is that from iminoesters and hydrazine. Cf. *A. Pinner*, Liebigs Ann. Chem. *297*, 221 (1897), and [2].

[2] *W. Oberhummer*, Mh. Chem. *63*, 285 (1933).

[3] Cf. *T. Kauffmann, C. Kosel*, and *D. Wolf*, Chem. Ber. *95*, 1540 (1962).

[4] *H. Henkler*, Ph. D. thesis, Technische Hochschule Darmstadt, 1962.

SO_2-Substituted Iron Carbonyls

By Dr. E. H. Braye and Dr. W. Hübel

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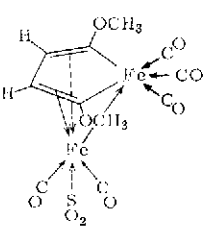
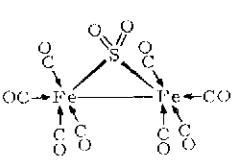
Carbon monoxide ligands of iron carbonyl compounds can be substituted by SO_2. Thus, on ultraviolet irradiation (125 watt lamp) of a solution of 3 g of 1,1,1-tricarbonyl-2,5-dimethoxyferracyclopentadiene-π-tricarbonyliron *(1)* [1] in 100 ml of boiling sulfur dioxide for one day, an orange-red complex *(2)* is formed in 55 % yield. Compound *(2)* melts with decomposition at 155–156 °C (from CH_2Cl_2), is insoluble in ether, and is decomposed by tetrahydrofuran or acetonitrile. Analyses show that in *(2)* one CO-group of the starting complex is replaced by SO_2. By analogy with $Fe_2(CO)_5P(C_6H_5)_3(C_6H_5C{\equiv}CC_6H_5)_2$ [2], it is assumed that the substitution has taken place on the π-linked $Fe(CO)_3$-group.



(2)



(3)

Enneacarbonyldiiron, $Fe_2(CO)_9$ reacts with sulfur dioxide even without irradiation to give the yellow compound $Fe_2(CO)_8SO_2$ *(3)*. The reaction may be carried out in petroleum ether by bubbling SO_2 through the liquid (yield *ca.* 18 %) or in liquid SO_2 at −10 °C or in a sealed tube at 20 °C (yields 7 and 18 % respectively). $Fe_3S_2(CO)_9$ [3] and small amounts of a red iron carbonyl complex decomposing at 139–141 °C are also formed. In the chromatographic separation of the reaction products on silica gel, *(3)* is eluted by CH_2Cl_2. Reaction between $Fe(CO)_5$ and SO_2 at 50 °C yields only small amounts of *(3)*. Compound *(3)* decomposes at

120–125 °C without melting and is moderately soluble in common organic solvents; it crystallizes readily from CH_2Cl_2. The structure proposed for *(3)* is in agreement with its simple infrared spectrum: terminal CO-groups absorb at 2137, 2092, 2070, 2058, and 2024 cm^{-1}, the SO_2-group at 1209 and 1048 cm^{-1}.

SO_2 is a weaker electron donor than carbon monoxide. This is confirmed by the lower stability of *(2)* compared with *(1)* and by the fact that the CO-stretching frequencies of *(2)* and *(3)* are higher than those of the corresponding unsubstituted carbonyl compounds.

Received, March 7th, 1963 [Z 461/284 IE]

[1] *H. W. Sternberg, R. A. Friedel, R. Markby,* and *I. Wender,* J. Amer. chem. Soc. *78*, 3621 (1956); regarding structure, cf. *A. A. Hock* and *O. S. Mills,* Acta crystallogr. *14*, 139 (1961).

[2] *E. Weiss, W. Hübel,* and *R. Merényi,* Chem. Ber. *95*, 1155 (1962).

[3] *W. Hieber* and *J. Gruber,* Z. anorg. allg. Chem. *296*, 91 (1958).

The Reactivity of Alkylaminoarsanes

By Dr. H. J. Vetter, H. Strametz, and Dr. H. Nöth

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der Universität München (Germany)

Transamination of $As[N(CH_3)_2]_3$ *(1)* [1] with secondary amines HNR_2 proceeds faster as the bulk of R decreases. With piperidine in boiling benzene, reaction (a) is complcted within 3 hours, but interaction with excess $HN(C_2H_5)_2$ or $HN(C_4H_9)_2$ requires longer heating.

$$As[N(CH_3)_2]_3 + 3\ HNR_2 \rightarrow As(NR_2)_3 + 3\ (CH_3)_2NH \qquad (a)$$
(1)

The following aminoarsanes are accessible in good yields by this route: $As[N(C_2H_5)_2]_3$ [1], b.p. 73 °C/0.5 mm; n_D^{20} = 1.4839; $As(NC_5H_{10})_3$, b.p. 139–142 °C/0.01 mm, m.p. 49 to 51 °C; and $As[N(n\text{-}C_4H_9)_2]_3$, b.p. 159–161 °C/0.01 mm, n_D^{20} = 1.4789. These react with carbon disulfide to give tris(dialkyldithiocarbamidato)arsanes [2], $As[S\ C(S)\text{–}NR_2]_3$ (R = CH_3, m.p. 240 °C; R = n-C_4H_9, m.p. 124 °C; R_2 = $-(CH_2)_5-$, m.p. 230 °C). The rate of reaction decreases rapidly in the series $N(CH_3)_2 > NC_5H_{10} > N(C_4H_9)_2$, which indicates the influence of steric factors.

Transamination of *(1)* with primary amines [3] yields cyclic aminoarsanes. The nature and size of the rings depend mainly on steric effects. Thus, reaction of *(1)* with bulky t-butylamine proceeds, (in contrast to the reaction with n-$C_4H_9NH_2$ [3]) by way of $(CH_3)_2NAs(t\text{-}C_4H_9NH)_2$ (b. p. 67 °C/0.01 mm, n_D^{20} = 1.4717), to a stable dimer, dimethylamino-t-butyliminoarsane *(2)*, b.p. 111–113 °C/0.5 mm, n_D^{25} = 1.5148.

(b)
$$2\ As[N(CH_3)_2]_3 + 2\ t\text{-}C_4H_9NH_2 \xrightarrow{-4\ (CH_3)_2NH} 2\ (CH_3)_2NAsCl_2 + 2\ t\text{-}C_4H_9NH_2 + 4\ N(C_2H_5)_3 \xrightarrow{-4\ (C_2H_5)_3N\cdot HCl} [t\text{-}C_4H_9N{=}As\text{–}N(CH_3)_2]_2$$
(2)

Dimeric t-butylamino-t-butyliminoarsane, b. p. 125 °C/0.01 mm, m. p. 80–85 °C cannot be obtained by transamination, but is readily prepared according to equation (c).

$$2\ AsCl_3 + 10\ t\text{-}C_4H_9NH_2 \rightarrow \underset{\substack{t\text{-}C_4H_9\text{–}N\text{–}As\text{–}NHC_4H_9\text{-}t \\ (3)}}{t\text{-}C_4H_9NH\text{–}As\text{–}N\text{–}C_4H_9\text{-}t} + 6\ t\text{-}C_4H_9NH_2\cdot HCl \qquad (c)$$

Hydrochloric acid splits the As–N bonds in *(2)* and *(3)* selectively. When used in stoichiometric quantities, it affects the exocyclic As–N bonds preferentially, and produces dimeric t-butylimino-chloroarsane m.p. 61–64 °C according to equation (d) [4].

$$(t\text{-}C_4H_9N{=}As\text{–}NR_2)_2 + 4\ HCl \rightarrow (t\text{-}C_4H_9N{=}AsCl)_2 + 2\ R_2NH\cdot HCl \qquad (d)$$

Received, March 11th, 1963 [Z 464/291 IE]

[1] *G. Kamai* and *Z. L. Khisamova,* Doklady Akad. Nauk SSSR *105*, 489 (1955).

[2] *L. Bourgeoise* and *J. Bolle,* Mém. Serv. chim. Etat *34*, 411 (1948).

[3] *H. J. Vetter* and *H. Nöth,* Angew. Chem. internat. Edit. *1*, 663 (1962).

[4] *G. Ohlah* and *A. Oswald,* Canad. J. Chem. *38*, 1428 (1960).

A Simple Method for the Preparation of Ethers from Phenols

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der Universität Kiel (Germany)

Phenols form aryl alkyl ethers when treated with primary alcohols in the presence of dicyclohexylcarbodiimide [1]. Originally [1] it was stated that room temperature and an inert solvent are required.

Considerably better results are obtained when the reagents are heated together at 100–110 °C in the absence of solvent. The yields of ether after 24 hours (Table 1) lie in the region of 84–91 % for *m*- and *p*-substituted phenols. *o*-Substituted phenols require 2–4 days heating before yields of the same order are obtained. The ethers are isolated from the reaction mixture by chromatography on acidic activated alumina. Using n-pentane/methylene chloride as eluant, the ether is in the first fraction in a state of extraordinary purity [2]. After removal of the solvent, the crystalline ethers have the correct melting point; even veratrol (m.p. 22.5 °C) is obtained in crystalline form. Liquid ethers are also completely pure without further distillation (refractive index).

Table 1. Yields of phenolic ethers by the carbodiimide method at 100 to 110 °C. In each case, 1.0 mole of phenol, 1.2 mole of alcohol and 1.1 mole of dicyclohexylcarbodiimide were reacted together in a sealed tube

	Benzyl alcohol	Methanol	Time of reaction [days]
Phenol	91	84	1
p-Methoxyphenol	91	88	1
m-Methoxyphenol	85	87	1
Guaiacol	78	76	4
p-Cresol	90	87	1
m-Cresol	84	85	1
o-Cresol	85	86	2

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[1] *E. Vowinkel,* Chem. Ber. *95*, 2997 (1962).

[2] After a long interval, a second fraction consisting of unreacted alcohol comes off the column. Phenol residues, carbodiimide, and the *N,N'*-dicyclohexylurea formed, as well as *O*-aryl ethers of *N,N'*-dicyclohexylisourea remain at the top of the column.

Coulometric Micro and Ultramicro Determination of Hydronium Capacities of Ion Exchangers

By Dr. B. Sansoni

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Hydrogen ions are eluted from the H^+-form of a cation exchanger with a concentrated solution of a neutral sodium salt according to:

$$H^+\text{-resin} + Na^+ \rightleftharpoons Na^+\text{-resin} + H^+.$$

The hydronium ions in even very small volumes of the eluate can be removed continuously from the equilibrium by hydroxyl ions produced coulometrically [1]. This allows simple but sensitive and accurate determinations of the hydronium capacities of ion exchangers.

Nitrogen is bubbled through 10 ml of a 1 N solution of sodium chloride in a micro cell equipped with a generating electrode (Pt, 1 cm^2), a micro glass electrode, and a salt bridge (agar-agar/saturated potassium chloride solution) linked to an external reference electrode (platinum in 0.2 N sodium chloride). The solution is titrated to pH 6.00 using a coulometer E 211 (Metrohm). After adding the H^+-form of the ion exchanger, it is again titrated to this pH with 0.03 to 10 mamp [2].

The capacities determined for a strongly acid ion exchanger (Lewatit S 100, hydronium form, 1–150 mg) agreed with the values obtained volumetrically using 1.25 g of resin according to [3]. The relative standard deviation of a single value [4] in 24 determinations with 7.5–150 mg was found to be ± 0.86 to ± 0.04 %. This is more accurate than the ± 3.5 % found for 8 volumetric macro determinations [2].

The coulometric method makes it possible to determine the hydronium capacities of single resin beads of sizes down to 0.2 mm diameter. Capacities of 13×10^{-9} to 53×10^{-9} equivalents per bead or 2.4-6.3 micro equivalents per mm^3 of spherical bead were found for the hydronium form of Dowex 50W X2 (0.20–0.25 mm in diameter, 90 determinations). The relative standard deviations of single values of the volume capacities lay between ± 12 and ± 54 %, and those of the average between ± 1.3 and ± 5.7 % [2]. By way of comparison, the former values for cobalt capacities were ± 3.0 to ± 6.1 %, when measured radiometrically with cobalt-60 on 87 beads. The greater fluctuation of the H^+-values compared to those of Co^{2+} is due partly to the lower precision of the coulometric method and partly to actual variations in the occupation of surface sites with hydronium ions.

The determination of the hydronium capacity of a single bead of resin of 0.5-0.2 mm diameter is an instructive lecture demonstration of the sensitivity of coulometric titrations.

Received, December 7th, 1962 [Z 406/282 IE]

[1] *J. J. Lingane:* Electroanalytical Chemistry. 2nd Edit., Interscience, New York 1958; *K. Abresch* and *L. Classen:* Die coulometrische Analyse. Verlag Chemie, Weinheim/Bergstraße, 1961.

[2] To be published in detail in Z. analyt. Chem.; measurements made in collaboration with *H. Schiemann.*

[3] *S. Fisher* and *R. Kunin,* Analytic. Chem. *27,* 1191 (1955).

[4] *G. Gottschalk:* Statistik in der quantitativen chemischen Analyse. Enke-Verlag, Stuttgart 1962.

1-Chloroborolanes

By Dr. R. Köster and Dr. G. Benedikt

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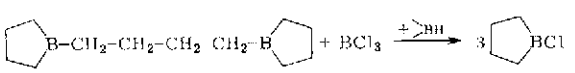
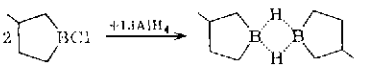
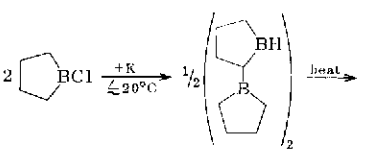
B-Chloroborolanes are obtained in about 90 % yield from α,ω-diborolanylalkanes [1] and boron trichloride (equimolar proportions) in the presence of BH-compounds [2], *e.g.* bisborolane [3], at 120–140 °C.

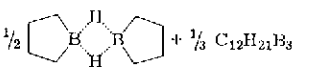


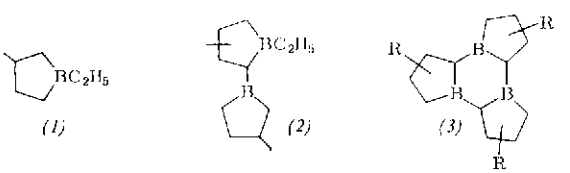
The compounds can be distilled at atmospheric pressure without decomposition at bath temperatures of up to 200 °C. 1-Chloroborolane (b.p. 96–100 °C) crystallizes after distillation, but 1-chloro-3-methylborolane (b.p. 110–112 °C) is obtained in the solid form only by cooling the distillate rapidly to −49 °C. Generally the liquid is initially mobile but slowly becomes very viscous at room temperature. The polymeric compounds formed which may involve ring and chain structures, depolymerize again in the presence of BH-compounds or on heating. In dilute solutions, *e.g.* in cyclohexane or benzene, the compounds are monomeric (cryoscopic molecular weight determination). With $LiAlH_4$, 1-chloroborolanes give bis-borolanes [3] in high yields.



Dehalogenation, *e.g.* with Na/K alloy at room temperature in hexane, also gives BH-compounds. Besides bisborolane ($\nu_{max(BH_2B)}$ = 1612 cm^{-1}), 2-borolanylborolane ($\nu_{max(BH_2B)}$ = 1575 cm^{-1}) is also formed. Starting from 1-chloro-3-methylborolane, a trimer of molecular formula $C_{15}H_{27}B_3$ can also be detected in the mixture of products by mass spectrometry. These boron hydrides (*e.g.* bis-borolanes above 110 °C) react stepwise with ethylene to give the *B*-ethylborolanes *(1)* and *(2)*.







(1) *(2)* *(3)*

R = CH_3; b.p. 85 °C/0,3 mm

In the presence of BH-compounds, or on heating after dehydroboration, *(2)* disproportionates into *B*-ethylborolane and high-boiling compounds with three boron atoms; we assume a structure corresponding with *(3)*.

Similar products are formed on dehalogenation of dialkylchloroboranes with Na/K-alloy; a compound proposed previously, potassium di-n-butylborane [4], could not be obtained. Under very mild conditions, at first BH-compounds are obtained which are soluble in hydrocarbons and ether ($\nu_{max(BH_2B)}$ = 1565 cm^{-1}). These are then transformed into sparingly soluble complexes ($\nu_{max(BH)}$ = 1900–2050 cm^{-1}, broad), which on deuterolysis afford 94 % HD besides 6 % D_2. This precludes the presence of essential amounts of compounds with B-K bonds.

Received, February 14th, 1963 [Z 444/274 IE]

[1] *R. Köster,* Angew. Chem. *71,* 519 (1959).

[2] *R. Köster,* Angew. Chem. *73,* 66 (1961).

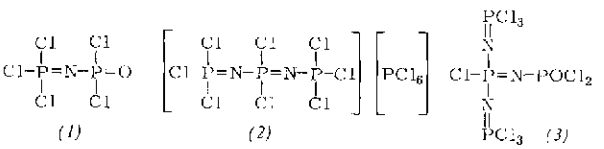
[3] *R. Köster,* Angew. Chem. *72,* 626 (1960).

[4] *R. Auten* and *C. Kraus,* J. Amer. chem. Soc. *74,* 3398 (1952).

Recent Investigations of Phosphorus-Nitrogen Compounds (N.M.R. Measurements)

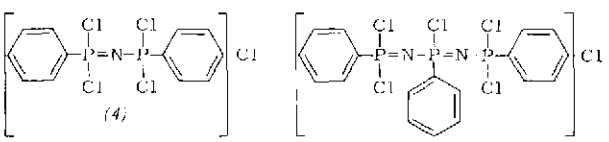
Ekkehard Fluck, Heidelberg (Germany)

The structures of compounds of elementary compositions P_2NOCl_5 *(1)*, P_2NCl_7 *(2)*, and $P_4N_3OCl_9$ *(3)* were clarified by measuring the nuclear magnetic resonance of the ^{31}P atom.

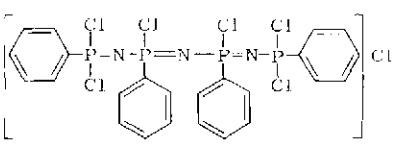


(1) *(2)* *(3)*

N. M. R. spectra of ^{31}P were also used to determine the qualitative and quantitative compositions of the complex reaction mixture which is obtained when S_4N_4 reacts with $C_6H_5PCl_2$. This mixture contains the compounds *(4)–(7)*, so far unknown, in addition to phenyldichloro-phosphine sulfide *(8)*, the main products being compounds *(4)*, *(7)*, and *(8)*. Compound *(4)* can also be obtained either by treating



(4) *(5)*



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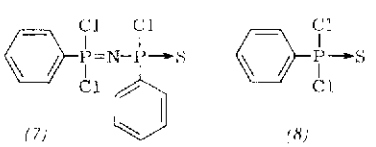
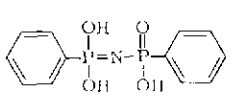


(7)

(8)

$C_6H_5PCl_2$ with NCl_3 (in the presence of PCl_5, the corresponding hexachlorophosphate is obtained), or by treating phenylphosphorus tetrachloride with ammonium chloride. Starting from *(4)*, the hitherto unknown free acid *(9)* is obtained by hydrolysis, its trichloride *(10)* by reaction of *(4)* with SO_2,



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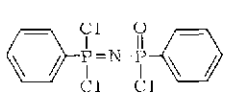

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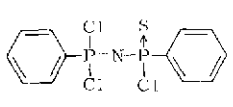

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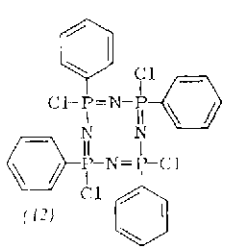


(12)

and the trichloride of the monothioimidodiphenyldiphosphonic acid *(11)* by reaction of *(4)* with H_2S. On heating, compound *(10)* splits into $C_6H_5P(O)Cl_2$ and phenylphosphorus nitrilochloride, which can partly be identified in the form of its tetramer *(12)* and partly in the form of a chain polymer $[C_6H_5PClN]_x$. From the latter a network polymer with oxygen bridges and an average composition of $[(C_6H_5)_6P_6N_6Cl_4O]_x$ can be obtained by partial hydrolysis.

[Inorganic Chemistry Colloquium at the Technische Hochschule Aachen (Germany), January 15th, 1963] [VB 680/71 IE]

Some New Aspects of Substitution in Higher Paraffins

F. Asinger, Aachen (Germany)

On monosubstitution of high molecular-weight, straight-chain paraffin hydrocarbons, the substituent is distributed statistically along the carbon chain, as experiments on chlorination, nitration, and chlorosulfonation have shown. Less substitution occurs at the ends of the molecule, on account of the reduced reactivity of the primary hydrogen atoms of the methyl group. Elucidation of the isomer proportions obtaining in disubstitutions has now been undertaken, utilizing chlorosulfonation and nitration reactions. n-Hexane-1-sulfonyl chloride was used as starting material for the chlorosulfonation, and 1-nitro-n-octane for the nitration. The use of these compounds, which already contain one substituent in a known position, reduces the number of possible disubstitution products.

The disulfonyl chlorides were thermally desulfurised to give dichlorides. It was established, that the chlorine atoms in these occupy the same positions on the same carbon atoms to which the sulfonyl chloride groups were previously attached. The dichlorides were determined quantitatively by gas chromatography. It was found that no geminal or vicinal disubstitution occurs, and that even 1,3-disubstitution is very strongly hindered; otherwise, statistical distribution of the newly introduced sulfonyl chloride groups along the carbon chain is observed.

A similar situation occurs with regard to the chlorination of n-hexane-1-sulfonyl chloride, a reaction which is known to occur in an analogous manner to chlorosulfonation. As expected, 1,3-disubstitution is not as strongly hindered here as in chlorosulfonation.

In the direct nitration of 1-nitro-n-octane, too, no geminal or vicinal disubstitution occurs. In contrast to chlorosulfonation, disubstitution in this case is also hindered at carbon atom 4. Only after the fifth carbon atom can an almost statistical distribution of the newly introduced substituent again be claimed.

The position of entry of the second nitro group was again determined by gas chromatography. The mixed 1,x-dinitro-n-octanes were converted by the Nef reaction and subsequent oxidation with potassium permanganate, or by treatment of the disodium salts suspended in chloroform with excess ozone, into the corresponding ketocaprylic acids, all of which were also prepared synthetically, and separated by gas chromatography in the form of their methyl esters.

[GDCh-Ortsverband Essen (Germany), December 13th, 1962] [VB 681/72 IE]

The Course of Propionic Acid Fermentation

Harland G. Wood, Cleveland, Ohio (U.S.A.)

Two new enzymatic reactions were described. The first is catalysed by phosphoenolpyruvic carboxytransphosphorylase

(1) CO_2 + phosphate + $H_2C{=}COPO_3H_2{-}COOH \rightleftharpoons$ $HOOCCH_2COCOOH$ + pyrophosphate

and is the reaction by which CO_2 is fixed in propionic acid fermentation. The reaction from the right to the left is

unique in that pyrophosphate is converted into high energy phosphoenolpyruvate and made available for ATP synthesis. In addition it is catalysed by a non-biotin enzyme. The second reaction (2) is catalysed by oxaloacetic transcarboxylase.

(2) $HOOCCH_2COCOOH + H_3CCH_2COSCoA \rightleftharpoons H_3CCOCOOH + H_3C{-}CH(COOH){-}COSCoA$

Acetyl-CoA or butyryl-CoA may be substituted for propionyl-CoA yielding malonyl-CoA or ethylmalonyl-CoA, respectively. Reaction (2) is unique in that it permits carboxylation with oxaloacetate and does not involve ATP or CO_2. The enzyme involved in reaction (2) contains biotin with a chemical role (reaction 3) that resembles that found in certain CO_2-fixation reactions by *Lynen*, *Knappe* and coworkers.

(3a) Enz-biotin + oxaloacetate $\rightleftharpoons$ Enz-biotin-CO_2 + pyruvate

(3b) Enz-biotin-CO_2 + propionyl-CoA $\rightleftharpoons$ Enz-biotin + Methyl-malonyl-CoA

Enzyme-biotin-$^{14}CO_2$ was prepared using reaction (3b). The complex obtained was labile but was stabilized by esterification with diazomethane. Subsequent digestion with pronase yielded radioactive *N*-methoxycarbonylbiocytin, which was converted into radioactive *N*-methoxycarbonylbiotin and lysine when hydrolysed with biotinidase. Thus, the biotin in this transcarboxylase is attached to lysine and serves as a carboxyl-transferring agent, the CO_2 being linked as carboxyl at the 1'-N of the biotin. There was no transfer of the ureido carbon as proposed by *Wakil*. The equilibrium of reaction (3b) favors formation of Enz-biotin-CO_2. A third enzyme, methylmalonyl isomerase, has been isolated and catalyses reaction (4).

(4) $H_3CCH(COSCoA)COOH \rightleftharpoons COSCoA{-}CH_2CH_2COOH$

The mechanism of reaction (4) was investigated by mass spectroscopic analysis of the succinyl-CoA formed from an equal mixture of $^{13}CH_3{-}CH(COOH)^{13}COSCoA$ and $^{12}CH_3CH(COOH)^{12}COSCoA$. It was shown in this way that the transfer of COSCoA occurs by an intramolecular reaction. The role of these reactions in propionate formation is as follows.

$H_3CCOCOOH + H_3C{-}CH(COOH){-}COSCoA \rightleftharpoons HOOCCH_2COCOOH + H_3CCH_2COSCoA$

$HOOCCH_2COCOOH + 4\,H \rightarrow HOOCCH_2CH_2COOH$

$H_3CCH_2COSCoA + HOOCCH_2CH_2COOH \rightleftharpoons H_3CCH_2COOH + HOOCCH_2CH_2COSCoA$

$HOOCCH_2CH_2COSCoA \rightleftharpoons CH_3CH(COSCoA){-}COOH$

Sum: Pyruvate + 4 H → propionate + H_2O

Fixation of CO_2 by reaction (*1*) results, in addition, in an accumulation of succinate.

[GDCh-Ortsverband München (Germany), Dec. 11th, 1962] [VB 678/70 IE]

Investigation of Surface Oxides of Carbon

H. P. Boehm, Heidelberg (Germany)

Microcrystalline black carbon in the form of sugar charcoal was oxidized with O_2 at about 420 °C. The resulting surface oxides (or hydroxides in the presence of water) were acidic and bound mainly to the edges of the hexagonal carbon layers. It was demonstrated by neutralization with bases of various strengths ($NaHCO_3$, Na_2CO_3, NaOH, $NaOC_2H_5$) that the acidic groups had different acidities. Equivalent amounts of four functions of different acid strengths were present. It is assumed that these acidic groups are components of a larger grouping.

The acidic groups were characterized more precisely by further reactions, *e.g.* by methylation with diazomethane and determination of the hydrolyzable methoxyl groups, by reaction with $SOCl_2$, NH_3, or dinitrofluorobenzene. The number of groups reacting was always equivalent to one of the neutralization values. An attempt was made to allocate the different acidities into distinct functional groups. It is assumed that free carboxyl groups, lactones of the fluoroscein type, and phenolic hydroxyl groups are present.

On treating diamond powder with oxidizing agents, *e.g.* sodium hypochlorite, acidic surface oxides were again obtained, the diamond becoming hydrophilic. Indications of the presence of carboxyl and tertiary hydroxyl groups were found. On the other hand, diamond which was treated with NO_2 gas reacted as a base. When diamond powder was heated to 800 °C at an O_2 partial pressure of ca. 10^{-2} mm. Hg, blackening occured. This discoloration was due to transformation of diamond into black microcrystalline carbon on the surface. The presence of small amounts of O_2 is necessary for this to occur. The fact that this was black graphite-like carbon was proved by means of its catalytic activity in the formation of HBr from its elements.

[Anorganisch-Chemisches Institut der Universität Heidelberg (Germany), January 22nd, 1963] [VB 690a/76 IE]

Investigations on the Regeneration of the Collagen Molecule

K. Kühn, Heidelberg (Germany)

The collagen molecule is a rod 2800 Å long with a diameter of 14 Å and consists of three polypeptide chains intertwined into a three-chain helix. The question investigated is whether a cell-controlled reaction must be assumed in order to account for the formation of the complicated collagen structure from the three 2800 Å polypeptide chains or whether association of the three chains to form the ordered helix occurs automatically and is governed only by the primary structure of the protein.

Neutral-salt soluble collagen, which has molecules which do not exhibit any intramolecular crosslinks, was heated at 38 °C in a citrate buffer at pH 3.7 for 90 minutes. The molecules dissociated completely into the three chains. The solution was subsequently cooled slowly to 4 °C over a period of a week. Electron-microscopic examination of the regenerated solution revealed the rigid rods of the renatured collagen together with particles which were not present in a rod-like form. By treating the solution with trypsin, which does not attack native collagen molecules, any incompletely regenerated particles were degraded and eliminated. The yield of trypsin-resistant collagen was about 50%. The trypsin-resistant molecules are indistinguishable in their behaviour from native, non-denaturated collagen. They have the same temperature of denaturation and form fibrils and long-spacing segments identical to those of native collagen.

[Chemisches Institut der Universität Heidelberg (Germany), January 22nd, 1963] [VB 690b/78 IE]

Kinetics and Poisoning in Ammonia Synthesis

R. Brill, Berlin-Dahlem (read by *H. Schaefer*)

Non or singly promoted (Al_2O_3) catalysts for ammonia synthesis were poisoned stepwise by small increments of H_2S. These experiments showed that poisoning is a slow process with a velocity determined by the rate of diffusion of the poison chemisorbed on the catalyst's surface. Promoted catalysts can tolerate more poison than non-promoted ones. The activation energy for the formation of ammonia is not altered by poisoning in either promoted or non-promoted catalysts. The poisoning experiments give excellent confirmation to the rate equations set up by *Ozaki*,

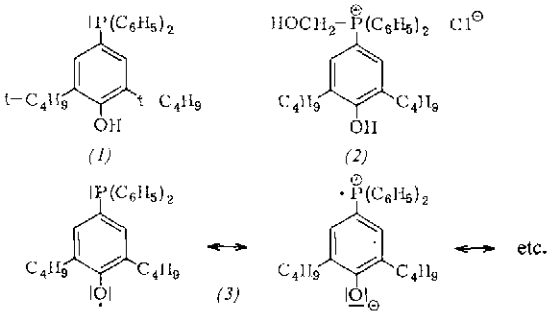
Taylor, and *Boudart* [1] for small yields of ammonia between 250 and 300 °C. It is shown that changes of the Fermi level, such as caused by poisoning or alloy formation between iron and aluminum, do not influence the activity of the catalysts. The results obtained can best be explained by assumption of active centres with roughly equal activation energies.

[GDCh-Ortsverband Münster (Germany),
February 18th, 1963] [VB 688/77 IE]

[1] *Ozaki, Taylor*, and *Boudart*, Proc. Roy. Soc. (London) *258*, 47 (1960).

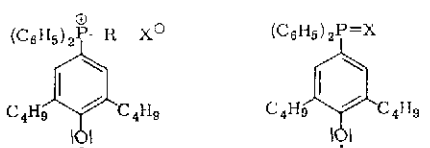
SELECTED ABSTRACTS

Free radicals containing phosphorus have been prepared by *Eugen Müller, H. Eggensperger*, and *K. Scheffler*. They confirmed the presence of these radicals by electron spin resonance spectroscopy. Their starting material was (3,5-di-t-butyl-4-hydroxyphenyl)diphenylphosphine *(1)*, which is accessible from potassium diphenylphosphine and 4-iodo-2,6-t-butylphenol. Compound *(1)* is extremely sensitive to air and was therefore transformed into the hydroxymethylphosphonium chloride *(2)* with formaldehyde and hydrochloric acid; it can then be liberated from this medium as required with dilute NaOH. Dehydrogenation of *(1)* with $K_3Fe(CN)_6$ gives a brilliant red radical *(3)*, which is soluble in benzene. Its ESR spectrum consists of two equally strong 1:2:1 triplets. The three lines of each triplet arise from interaction of the unpaired electron with the nuclear spins of the two protons in the *meta*-position, while the doubling of the triplet is caused by the ^{31}P nucleus ($I = 1/2$).



(1) *(2)* *(3)*

If *(2)* is dehydrogenated with 4-methoxycarbonyl-2,6-di-t-butylphenoxyl, an equilibrium mixture is obtained which contains the phsophonium radical *(4)*. Ethylphosphonium fluoroborate *(5)*, which is formed from *(1)* and triethyloxonium fluoroborate, can also be dehydrogenated to give the phosphonium radical *(6)*. Compound *(1)* yields phosphine sulfide *(7)* with sulfur, and phosphine oxide *(8)* with peracetic acid. Both can be dehydrogenated to the corresponding radicals *(9)*, which is deep blue, and *(10)*, which is green. The ESR



(4): R = CH_2OH, X = Cl
(6): R = C_2H_5 , X = BF_4

(9): X = S
(10): X = O

(and further resonance structures)

spectra show two triplet states each also for *(4)*, *(6)*, *(9)*, and *(10)*. / Liebigs Ann. Chem. *658*, 103 (1962) / –Ko. [Rd 420/122 IE]

Organosilicon compounds can be prepared radiochemically, according to a report by *A. V. Zimin, A. D. Verina, L. P. Sidorova*, and *A. V. Gubanova*. Mixtures of hydrochlorosilanes ($SiHCl_3$, SiH_2Cl_2, CH_3SiHCl_2, or $C_2H_5SiHCl_2$) and olefins, partly fluorinated olefins, benzene, or chlorobenzene were exposed to γ-radiation from a ^{60}Co source at 20 and 70 °C. High yields of organochlorosilanes of composition $RSiCl_3$ or R_2SiCl_2 (R = H, alkyl, aryl, or fluoroalkyl) were obtained. Maximum yields are obtained with a proportion of 1 molecule of olefin to each Si-H bond in the starting mixture. The high yields are explainable by the chain reaction character of the addition of olefin onto the Si-H bond. An increase in the reaction temperature from 20 to 70 °C led to an increase in yield only with alkyl- and dialkylchlorosilanes. / Dokl. Akad. Nauk USSR *144*, 576 (1962) / –Ko. [Rd 421/123 IE]

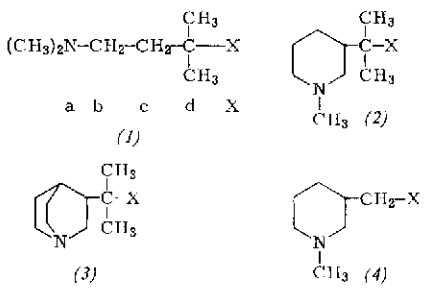
Manganese tetrafluoride, the first binary halide of tetravalent manganese, has been prepared by *R. Hoppe, W. Dähne*, and *W. Klemm*. MnF_3 was heated to above 400 °C in a stream of F_2, whereby MnF_4 volatilized off and was deposited on a cooled gold tube. MnF_2, $MnCl_2$, and $MnSO_4$ also ultimately form MnF_4 under these conditions, *via* MnF_3. Similarly, if red $LiMnF_5$ is heated in a stream of F_2, MnF_4 sublimes off, and a residue of yellow Li_2MnF_6 is left. MnF_4 is bright blue-grey, amorphous as judged by X-rays, and is highly reactive. Thus, it reacts extremely violently even with traces of water, and ignites in the presence of dry petroleum. MnF_4 obeys the Curie-Weiss law, and its magnetic moment is 3.82 Bohr magnetons, $\Theta \approx -10$ °C. The compound is relatively unstable even in a protective atmosphere or *in vacuo* and appears to possess a relatively high partial pressure of F_2 even at room temperature. / Liebigs Ann. Chem. *658*, 1 (1962) / –Ko. [Rd 422/124 IE]

The existence of hydrazinium(2+) ions, $N_2H_6^{2+}$, was detected by *H. Bock* by preparing hydrazinium(2+) salts, $N_2H_6(A)_2$ of complex acids HA (*e.g.* $HSbCl_6$ or HBF_4). According to the "adjacent charge rule" of *Pauling*, the existence of similar charges on neighbouring atoms is energetically unfavourable. By treating hydrazine dichloride $N_2H_4 \cdot 2\,HCl$ with antimony pentachloride, the hypothetical hydrazinium(2+) dihexachloroantimonate, $N_2H_6(SbCl_6)_2$, is formed, which reacts momentaneously on mixing with ethylene chloride with elimination of 1 mole of HCl and conversion into a hydrazinium(1+) hexachloroantimonate/antimony pentachloride double salt, $N_2H_5(SbCl_6) \cdot SbCl_5$. By introducing BF_3 into a solution of hydrazine difluoride, $N_2H_4 \cdot 2\,HF$, or hydrazinium(1+) tetrafluoroborate, $N_2H_5BF_4$, in anhydrous HF, hydrazinium(2+) ditetrafluoroborate, $N_2H_6(BF_4)_2$, precipitates, which is converted by heating over KOH into hydrazinium(1+) tetrafluoroborate/boron trifluoride, $N_2H_5(BF_4) \cdot BF_3$, with elimination of 1 mole of HF. / Z. Naturforsch. *17b*, 426 (1962) / –Ho. [Rd 435/125 IE]

The volatile odor essences of raspberries were isolated from 580 kg of fresh fruit and identified by *M. Winter* and *E. Sund*. The fruit was ground in an atmosphere low in oxygen, the resulting pulp was then immediately submitted to thin-layer steam distillation, and the distillate was extracted with ether. By fractional distillation of the extract, 0.02–0.003 % of an oil was obtained; strawberries yield 0.05 0.01‰ by the same technique. By absorption and partition chromatography of its 2,4-dinitrophenylhydrazones, the carbonyl fraction of the volatiles was separated into 14 aliphatic and alicyclic aldehydes and ketones: diacetyl, acetoin, acetaldehyde, acrolein, acetone, propanal, β,β-dimethylacrolein, 2-pentenal, *cis*-3-hexenal, 2-hexenal, 2-pentanone, hexanal, (+)-α-ionone, and β-ionone. By similar means, the 3,5-dinitrobenzoates of the alcohol fraction yielded 11 alcohols: *cis*-3-hexen-1-ol, 1-hexanol, ethanol, methanol, 3-methyl-3-buten-1-ol, 1-

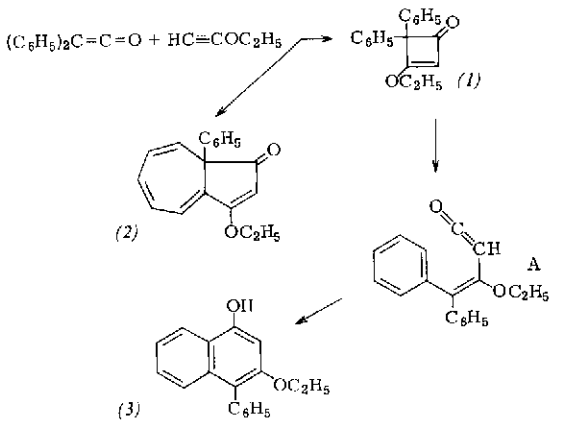
penten-3-ol, 1-pentanol, *trans*-2-buten-1-ol, 1-butanol, 3-methyl-2-buten-1-ol, and geraniol. Besides the alcohols and carbonyl compounds, ethyl acetate and other products were also found. / Helv. chim. Acta, *45*, 2186, 2195, 2212 (1962) / –Bs. [Rd 433/126 IE]

A fragmentation reaction a–b c–d–X → a–b + c=d + X was studied by *C. A. Grob* and *F. Ostermayer* using γ-aminoalkyl halides and arylsulfonates. With these it is possible to study the stereo-electronic prerequisites for reaction by using cyclic compounds and the inductive or mesomeric influence of "a" on the course of the reaction by using various *N*-substituted products. The compounds *(1)* to *(4)* were investigated in aqueous NaOH. The carbimonium ions which constitute the fragment a b undergo hydrolysis under the reaction conditions to give formaldehyde and secondary amines. By estimating the latter, the extent of the fragmentation can be ascertained.

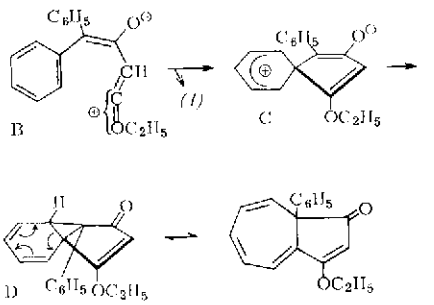


When X = Br, besides substitution (S_N) and 1,2-elimination, the amount of fragmentation estimated was 48 % with *(1)*, 60 % with *(2)*, and 62% with *(3)*; on the other hand, no fragmentation occurred with *(4)*. The results indicate the occurrence of a carbonium ion as an intermediate step in the fragmentation. In this respect, fragmentation presents another possibility for the stabilization of a carbonium ion in competition with elimination and substitution. / Helv. chim. Acta *45*, 1119 (1962) / –Bs. [Rd 434/127 IE]

Cycloaddition of ethoxyacetylene onto diphenylketene takes place at –25 °C to form 1-ethoxy-3-oxo-3,3a-dihydroazulene *(2)* and 1,1-diphenyl-2-ethoxycyclobut-2-en-4-one *(1)*, according to investigations of *J. Druey*, *E. F. Schenker*, and *R. B. Woodward*. On gently warming, *(1)* rearranges probably *via* the vinylketene *(4)* to 1-phenyl-2-ethoxy-4-hydroxy-



naphthalene *(3)*. The existence of a five-membered ring in *(2)* was ascertained by reduction, the existence of a seven-membered ring by oxidation to a five-membered ring, and the 1,2-relationship between the phenyl and keto groups and the 1,4-relationship between the phenyl and ethoxy groups by thermal rearrangement.



In the first step of the reaction, the ethoxyacetylene probably becomes associated with the carbonyl group of the diphenylketene. The zwitterion *(5)* affords in part the cyclobutenone *(1)* and in part a spirocarbonium ion *(6)*. The dihydroazulene *(2)* finally arises through the norcaradiene *(7)*. / Helv. chim. Acta *45*, 600 (1962) / –Ho. [Rd 436/128 IE]

BOOK REVIEWS

Landolt-Börnstein: Zahlenwerte und Funktionen aus Physik, Chemie, Astronomie, Geophysik und Technik (Numerical Data and Functions in Physics, Chemistry, Astronomy, Geophysics, and Technology), 6th Edition, Volume 2: Properties and States of Matter, Part 7: Electrical Properties II (Electrochemical Systems). Springer-Verlag, Berlin-Göttingen-Heidelberg, 1960. XII plus 959 pp., 405 illustrations, bound DM 478.– (about $120.–).

This seventh part of Volume II of the new edition [1] of Landolt-Börnstein contains data on electrical properties of electrochemical systems, *viz.* 1. electrical conductivities, 2. electromotive forces, and 3. equilibria in these systems. These general headings of the sizable volume, by themselves, give an idea of the importance this volume may have for the research chemist as well as the technical chemist, regardless of whether their problems relate to inorganic or organic chemistry.

The first and longest chapter contains 745 pages and is subdivided in turn into electrical conductivities of fused salts (*P. Drossbach*), of pure liquids (*K. Cruse*), of aqueous electrolytes (*H. Falkenhagen, G. Kelbg, E. Schmutzer*), and of non-aqueous solutions (*K. Cruse*). Furthermore, it contains a section on colloid chemistry summarizing data on electrophoretic mobility and ξ-potentials (*H. Strehlow*).

This chapter deals for example with the conductivities of mixtures of inorganic and organic salts, of numerous organic compounds, of inorganic and organic aqueous electrolytes, the conductivities of mixtures of electrolytes and the dependence of the conductivities of aqueous solutions on the frequency and field strength. The section on non-aqueous solutions contains conductivities both in inorganic and organic solvents and in solvent mixtures.

The method of arrangement and, especially in the case of aqueous and non-aqueous solutions, the insertion of small tables of contents giving further sub-divisions with page numbers at the beginning of each section makes it easy to obtain a clear survey of the very extensive subject matter. In the case of the organic solvents, for instance, a table of organic compounds is included that is clearly set out according to the number of carbon atoms, together with the page numbers. In the case of the solvent mixtures, there is a table showing the two components in two columns, again with the pertinent page numbers.

The second chapter (*P. Drossbach*) has 90 pages and tabulates reversible and irreversible potentials. Thus, it contains the values for the electromotive forces of galvanic elements and chains as well as standard potentials in aqueous solution, e.m.f.'s in non-aqueous solvents, and e.m.f.'s in fused salts.

Furthermore, irreversible potentials (over-voltages) in aqueous solutions and in melts are given here in the form of a literature survey.

The third chapter has 120 pages and deals with equilibria in electrochemical systems. The section on dissociation constants (*G. G. Grau*) of water and inorganic and organic compounds extends over 100 pages. The final section is made up by a long table of acid-alkali indicators (*R. Appel*) and a table of buffer mixtures (*G. G. Grau*).

The compilation of the numerical data contained in the present volume required a vast literature survey, as many numerical values are hidden away in papers that were not designed for the express purpose of determining constants, but to solve physico-chemical problems of a different nature. It would therefore not be surprising if, on checking a reference, the value given in the literature cannot occasionally be found. However, if the figure in question is contained in the tables, it will certainly be traceable, thanks to the excellent clarity of arrangement. The contributions to the volume of several well-known authors in the field of electrochemistry guarantees the best possible results. *R. Suhrmann* [NB 948/32 IE]

[1] Cf. Angew. Chem. *72*, 218 (1960).

Hochspannungselektrophorese, ihre Anwendungsmöglichkeiten für biochemische und klinisch-chemische Trennprobleme (High Voltage Electrophoresis, its Scope of Application for Biochemical and Clinico-chemical Separation Problems). By *R. Clotten* and *A. Clotten*, Georg Thieme Verlag, Stuttgart 1962, 1st Edition, XVI, 556 pp., 111 figures, 113 tables, price DM 98.– (about $25.).

In view of the fact that a series of books on paper electrophoresis is already available, is it now justifiable to publish an extensive work on a specialized subject such as that of high voltage electrophoresis? The reviewer believes that this question should be answered in the affirmative, since this method, which is now more than ten years old, has found worldwide use in the last few years, owing mainly to the successes it has achieved in the separation of peptides and in combination with paper-chromatography in "finger-printing". A monograph dealing with high voltage electrophoresis and summarizing its achievements to date is to be welcomed, especially as this method frequently makes possible a more efficient separation than any other and since it requires specialized equipment. The authors, working at the University Hospital in Freiburg (Germany), studied the application of high voltage electrophoresis to clinico-chemical problems for many years and achieved significant results in the analysis of low molecular-weight substances from tissue extracts and body fluids. Hence, they included in this book the practical experience accumulated from daily use of the method; as an example, the extensive table dealing with inherent and avoidable errors of the method might be cited.

The authors' intention of writing a book to enable separation experiments to be carried out and their results to be interpreted without consultation of the original literature is very commendable, especially as the method is widely used in clinical laboratories. However, as a result, nearly half of the book consists of the reproduction of material which, although critically selected here, is already known from handbooks of paper chromatography (coloration techniques, quantitative determinations). Indications are given to the reader that this or that coloration method was particularly successful in the laboratory and is to be recommended. In other chapters too (general, methods, results), the reader is aware that the book has emerged from practical experience.

Previously unpublished results obtained by the authors in the clinico-chemical field (not to mention the numerous illustrations and figures, some of them in color) contribute to the emergence of a nicely finished work which documents impressively the importance of high voltage electrophoresis. The inclusion of large tables dealing with the behavior of various groups of compounds (amino acids, peptides, porphyrines, alkaloids, pesticides, carbohydrates, vitamins, *etc.*) deserves special mention, as they greatly facilitate the handling of the book.

A bibliography containing 2500 references (up to 1961) and a carefully arranged index complete the book, which is printed in high quality and which is expected to be useful and stimulating not only to workers engaged in this particular field. In view of the qualities mentioned above, which are not detrimented by a few small mistakes and inaccuracies, widespread use of the book cannot only be hoped for, but can be predicted with certainty. *B. Kickhöfen* [NB 985/35 IE]

Mitteilungen aus den Forschungslaboratorien der AGFA Leverkusen-München (Communications from the Research Laboratories of AGFA Leverkusen-München) Vol. III. Springer Verlag, Berlin-Göttingen-Heidelberg. 1961. 1st Edit., VIII, 344 pp., 59 illustrations, 2 tables. DM 64.50 (about $16.–).

This third volume of communications from the Research Laboratories of Agfa AG. at Leverkusen and Munich is dedicated to Dr. *Fritz Albers*, who was for many years Head of the Agfa Photographic Paper Manufactory. As in previous volumes [1], the latest work on the subject of scientific photography carried out by Agfa is collected in the present one.

The series of articles opens with a description of the work of *E. Klein* and *R. Matejec* on "Unsolved Problems in the Theory of Elementary Photographic Processes". A very valuable estimation of the position in this field and an unusual abundance of literature references are presented. The same authors, with *H. Frieser*, then report on some investigations of these fundamental processes, including: "The Theory of the Density Curve and the Calculation of Sensitivity Distribution" and physical investigations concerning silver halide crystals.

The following articles by *J. Eggers* on problems of photographic developing are concerned, among other subjects, especially with the mechanism of color development and with the pH changes in photographic layers during development. Besides the work on the most diverse aspects of photography such as sensitometry, masking, reciprocity failure, spectral sensitisers, *etc.*, investigations on magnetophone tapes are also described. The book contains in all 24 contributions from 23 authors.

The most extensive dissertation in the volume, *viz.* "Color Couplers" by *W. Pelz*, deserves special mention. This provides a comprehensive summary of the present position in this important special subject.

The lay-out of the work is excellent, so that in appearance and content, this volume will be a worthy successor to those published earlier. *J. Eggert* [NB 970/33 IE]

[1] Cf. Angew. Chem. *68*, 598 (1956); *72*, 145 (1960).

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New Methods of Preparative Organic Chemistry

Syntheses Using Pyridinium Salts [*]

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This review discusses syntheses leading to a new type of N-vinylpyridinium salts, to novel anionocyanines, to aminophenazines and alloxazines, as well as to (aza-)dehydroquinolizinium, acridizinium, and morphanthridizinium salts. In addition, Mannich reactions and aminoalkylations at active methylene groups of cycloimmonium salts, and their reactions with amines are treated. The possibilities offered by the "Ortoleva-King" reaction are demonstrated using numerous examples, such as a new route leading to the yohimbine skeleton.

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Introduction [**]

The special nature of pyridinium cations allows them to be used in a great variety of syntheses. Their reactivity is due to the aromatic character of the pyridine heterocycle, to its basicity, and to the electron-attracting influence of the nitrogen atom in pyridine, which becomes even more pronounced in the pyridinium cation. The electrophilic effect of the nitrogen makes positions 2, 4, and 6 of the heterocycle relatively electropositive, so that they become susceptible to attack by nucleophiles such as cyanide or piperidyl anions. Attack by hydroxide ions yields substances called "pseudobases" after *Hantzsch*. If the nucleophile is attached to the nitrogen atom of a pyridinium, isoquinolinium or similar salt, ring closure to give a fused ring system, such as that of imidazopyridine, may occur. If the anion of a pyridinium salt is oxidizable, *i.e.* if it tends to donate electrons, then it can act as the nucleophile. A bathochromic shift is then observed in the absorption spectrum ("interionic mesomerism") [1].

A further consequence of the electron withdrawal from positions 2, 4, and 6 is the activation of the hydrogen atoms of methyl, benzyl, or other groups attached at these carbon atoms. This activation is due to the same causes as, and is of similar extent to, that of the hydrogen atoms in methyl and methylene ketones. This applies especially to quaternary salts such as α- and γ-picolinium salts.

[*] Communication No. 3. Communication No. 1: Angew. Chem. *65*, 605 (1953); Communication No. 2 (with *W. Zecher*): Angew. Chem. internat. Edit. *1*, 626 (1962).

[**] The following abbreviations are used in this paper:
Py$^+$ denotes
Ac denotes CH_3–CO–,
Ar′ denotes ,
ON–Ar′ denotes *p*-nitrosodimethylaniline,
Ph often denotes C_6H_5.
As long as anions such as $Br^\ominus$ and $ClO_4^\ominus$ do not participate in the reaction, they will often be omitted.

[1] *F. Kröhnke*, J. prakt. Chem. *6*, 235 (1958).

However, the hydrogen atoms of *N*-methyl and *N*-methylene groups also become activated. Numerous important syntheses using pyridinium salts are based on this activation phenomenon. These include syntheses of carboxylic acids, α-ketoaldehydes, and α-ketocarboxylic acids from methyl(ene) ketones (see CommunicationNo. 1). In typical cases, the pyridinium moiety is split off as pyridine during the reaction with the electrophilic agent. Finally, the ring may be opened on one or both sides of the pyridinium nitrogen, especially if the latter is bound to strongly electron-attracting groups. Such ring cleavages may be utilized in a variety of ways. Thus, cyanines, azulenes, enamines, and deoxybenzoins become accessible from pyridinium salts, often in a one-step synthesis.

None of the above properties is specific to pyridine alone or to the pyridinium cation only; almost all recur in other heterocyclic bases and their quaternary salts. Some are present even in open-chain oxonium and sulfonium salts and also, albeit faintly, in open-chain ammonium salts. The increase in the electropositive character of the α-position in the isoquinolinium or of the γ-position in the quinolinium or the acridinium cation, and the reactivity of the methyl group in quinaldine and in quinaldinium salts, for example, are even greater than the corresponding phenomena in the comparable pyridinium or picolinium salts. However, the peculiarities described here are present in the pyridinium cation to such an extent and in such a mutual balance that they are especially favorable for a variety of syntheses. Thus, the reactivity in alkaline solution of *N*-benzyl- and, especially, *N*-phenacyl- or *N*-cyanomethylpyridinium cations is similar to that of β-diketones and β-ketocarboxylic esters.

A comparative review of aromatic heterocycles and their quaternary salts, which would establish the special suitability of pyridinium salts for various syntheses, would be outside the scope of this article, hence, substitutions on the pyridinium ring [1a] and syntheses with pyridine-*N*-oxide are barely touched upon. In contrast to Communication No. 1, discussions of pyridinium betaines [2] and of "acid cleavage" and its preparative applications are also omitted [3].

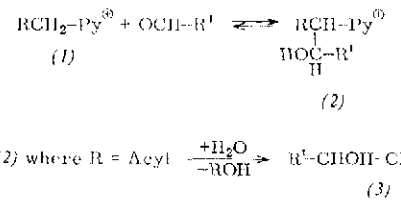
The future potentialities of syntheses using pyridinium salts cannot be predicted or defined at present. From the present situation, however, it seems that the synthesis of diverse new heterocyclic compounds from pyridinium salts may be the chief result of application of this new method.

A fourth communication (to appear shortly in this journal) will complete this review.

I. Syntheses via the Action of Carbonyl Compounds on Pyridinium Salts

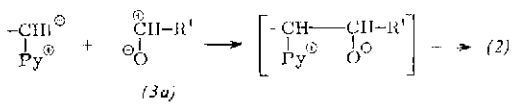
1. New Vinylpyridinium Salts

Aldehydes react reversibly in alkaline alcoholic solution with pyridinium salts containing an active methylene group *(1)* [4]. This reaction leads to pyridinium ethanols *(2)*.



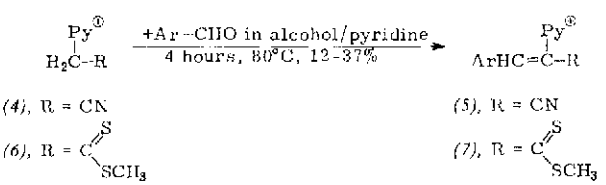
R′ may be H, alkyl, or (substituted) phenyl, and R may be H, (substituted) phenyl, $C_6H_5CH{=}CH{-}$, alkyl-OCO–, *etc.* If R is an acyl radical, then it is cleaved during the aldol condensation to give a pyridinium salt of formula *(3)*. This reaction is irreversible. Since formaldehyde reacts even in neutral solution – though more favorably in the presence of piperidine acetate – it is possible to trap the intermediate product *(2)* as its picrate (R = C_6H_5CO, R′ = H) by using an excess of aldehyde [5].

Combination of the reactants is favored by any increase in the electropositive nature of the carbon atom of the aldehyde group *(3a)* and vice versa. Thus, nitrobenzaldehydes give especially good yields, whereas *p*-

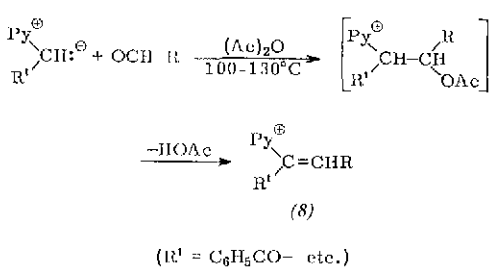


dimethylaminobenzaldehyde and particularly formamide do not react even with phenacylpyridinium bromide *(1)* under these conditions (R = C_6H_5CO).

Methylene groups attached to the pyridinium nitrogen and bound to especially strongly activating groups such as *(4)* and *(6)* even react with aromatic aldehydes in hot alcohol with only pyridine as the alkaline catalyst. The reaction yields the vinylpyridinium salts *(5)* and *(7)* [6].



On the other hand, aldehydes with carbonyl groups bonded to electron-donating groups, *e.g.*, *p*-dimethylaminobenzaldehyde, react well with pyridinium salts containing active methylene groups (especially *N*-phen-



(R′ = C_6H_5CO– etc.)

[1a] *K. Thomas* and *D. Jerchel*, Angew. Chem. *70*, 719 (1958).

[2] *F. Kröhnke*, Angew. Chem. *65*, 609 (1953).

[3] *F. Kröhnke*, Angew. Chem. *65*, 607 (1953).

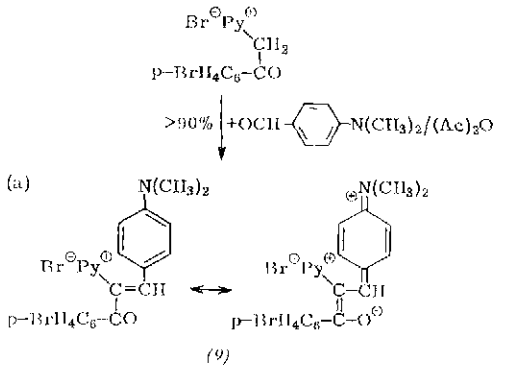
[4] *F. Kröhnke*, Angew. Chem. *65*, 617 (1953).

[5] *J. Curtze*, Diploma thesis, Universität Gießen, 1961, p. 48 et seq.

[6] *A. Peuser*, Ph.D. thesis, Universität Gießen, 1962, pp. 23 and 59 et seq. as well as 41 and 67 et seq.

acylpyridinium salts) when heated almost to the boil in acetic anhydride; the reaction proceeds even without addition of alkaline agents and yields vinylpyridinium salts *(8)* via their C-acyl derivatives, rather than pyridinium ethanols.

When *p*-dimethylaminobenzaldehyde is treated with *p*-bromophenacylpyridinium bromide in acetic anhydride at 130 °C, a vinylpyridinium salt *(9)* is obtained in over 90 % yield. The reaction does not, however, take place with *p*-nitrobenzaldehyde. The *p*-bromobenzoyl residue which participates in the resonance hybrid *(9)* is thus not split off.



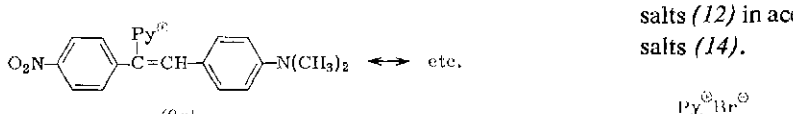
(9)

Preparation of 1-(p-dimethylaminophenyl)-2-pyridino-3-(p-bromophenyl)-1-propen-3-one bromide (9) [7].

A mixture of 164 mg (1.1 mmole) of *p*-dimethylaminobenzaldehyde and 356 mg (1 mmole) of *N*-(*p*-bromophenacyl)-pyridinium bromide in 3 ml of acetic anhydride is stirred for 15 minutes at 130 °C. Ether is carefully added to the clear yellow solution until crystallization starts. About 30 ml of ether is required for complete precipitation: 441 mg (90 %) of light orange crystalline rods are obtained. After recrystallization from a mixture of 25 parts ethanol and 5 parts ether, this product decomposes with vigorous effervescence at 267 to 268 °C.

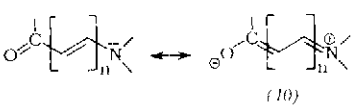
2. New Mero- and Anionocyanines

Under mild Perkin reaction conditions (17 hours, 85 °C), *p*-dimethylaminobenzaldehyde also reacts with *N*-*p*-nitrobenzylpyridinium bromide to give *(9a)* in 18 % yield [8].



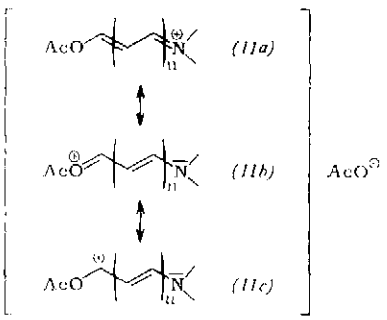
(9a)

The fact that *p*-chlorobenzaldehyde (64 % yield) and *p*-nitrobenzaldehyde (95 % yield in 1.5 hours at 130 °C [8a]) react more easily and more efficiently in the above reaction [8] indicates the predominance of the aldol-type reaction, corresponding to *(1)* → *(2)*. On the other hand, reaction according to equation (a) proceeds essentially by a somewhat different mechanism. *p*-Dimethylaminobenzaldehyde, *Zincke*'s aldehyde, etc. are phenylogous or vinylogous formamides and thus the enhancement of the electropositivity of the carbon atom in their carbonyl groups, which is necessary for aldol reactions, is considerably weakened by resonance. As a result, the dipolar resonance structure *(10)* governs their behavior. Acylation of the latter with acetic anhydride or with the acyl cation yields *(11)*, thus

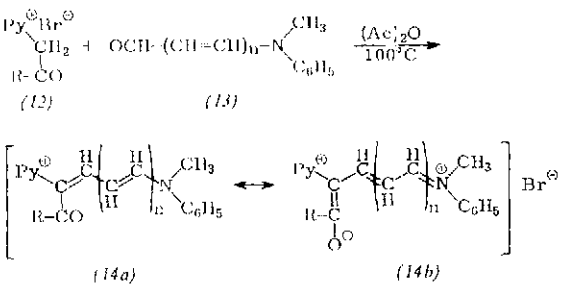


(10)

causing the negative charge on the oxygen atom to disappear. Consequently, the vinylogous formamide



re-acquires a full positive charge, and the resonance structure *(11c)* with its carbonium atom can react with the carbanion of the pyridinium salt. Phenyl substituents with (+I)-effects should also promote reaction of the phenylogous formamides. The process is analogous to the activation of vinylogous formamide by phosphorus oxychloride in the procedure of *Vilsmeier* and *Haack*. Here close analogies to that reaction, which has recently been reinterpreted and extended to perform some very elegant syntheses [9], can be identified. Thus, aldehyde reactions which fail to work with non-acylated formamides proceed even better than in the case of aldehydes of the *p*-nitrobenzaldehyde type. As a result, syntheses of new kinds of cyanines of the anionocyanine type have become possible [10]. Thus, 5-(*N*-methylanilino)-2,4-pentadienal (*Zincke*'s aldehyde *(13)*, where n = 2) reacts smoothly with acylalkylpyridinium salts *(12)* in acetic anhydride to give red vinylpyridinium salts *(14)*.



(14a) *(14b)*

[7] *K. Dickoré* and *F. Kröhnke*, Chem. Ber. *93*, 1072 (1960).

[8] *F. Kröhnke* and *M. Meyer-Delius*, Chem. Ber. *84*, 411 (1951), particularly pp. 422 and 420.

[8a] Experiment by *H. Ahlbrecht*, Diploma thesis, Universität Gießen, 1963.

[9] See especially the remarkable synthetic successes of *C. Jutz* using vinylogous formamides and the reaction mechanisms he proposed for them: Chem. Ber. *91*, 850 (1958); Angew. Chem. *70*, 270 (1958) and later publications.

[10] *K. Dickoré* and *F. Kröhnke*, Chem. Ber. *93*, 1071 (1960).

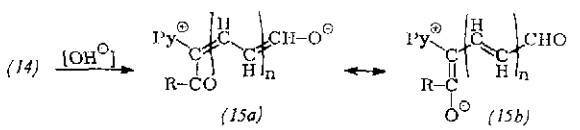
Preparation of 1-(N-methylanilino)-6-pyridinio-7-(p-bromophenyl)-1,3,5-heptatrien-7-one-bromide (14), where R = p-BrC$_6$H$_4$ and n = 2 [10]

A mixture of 357 mg (1 mmole) of *N*-(*p*-bromophenacyl)-pyridinium bromide *(12)*, where R = *p*-BrC$_6$H$_4$, and 30 ml of acetic anhydride is heated on a water bath until solution is complete, and then 206 mg (1 mmole + 10 % excess) of Zincke's aldehyde, 5-(*N*-methylanilino)-2, 4-pentadienal *(13)*, are added. The originally yellow solution immediately changes to red-brown and it is heated for a further 30 minutes on the water bath, meanwhile becoming clear red (Zincke's aldehyde alone becomes green in acetic anhydride). The reaction product is precipitated with about 250 ml of ether, the supernatant solution is decanted and the product which separates out and adheres to the walls of the glass reaction flask is washed repeatedly with ether, dissolved in some hot chloroform, and treated with charcoal; the solvent is then allowed to evaporate off slowly. Red rhombic platelets, still containing $^1/_3$ mole of HBr, crystallize out; the yield is 526 mg (96 %). When recrystallized from 20 parts of chloroform by cooling slowly, the salt melts at 172–173 °C. Relatively less acetic anhydride is used with larger batches, and the mixture is stirred until all the starting material dissolves; however, the yields are then lower.

Compounds of type *(14)* are quantitatively cleaved to aldehyde betaines *(15)* by dilute sodium hydroxide.

Preparation of 6-pyridino-7-(p-bromophenyl)-2,4,6-heptatrienal-7-oxide (15), where R = p-BrC$_6$H$_4$ and n = 2 [10]

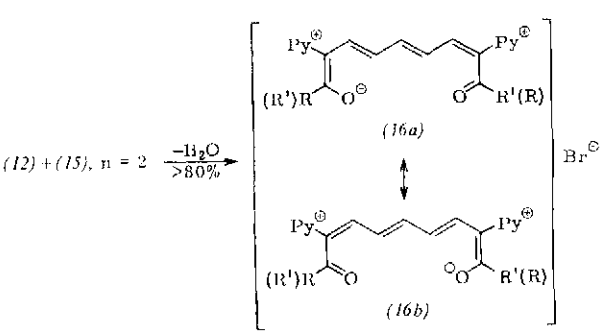
A deep red solution of 553 mg (1 mmole) of compound *(14)*, where R = *p*-BrC$_6$H$_4$ (still contains $^1/_3$ mole of HBr), in 2.5 ml of methanol is added to 50 ml of 10 % sodium hydroxide,



(15a) *(15b)*

which has been cooled to 0 °C. A color change to yellow-orange is observed, and soon extremely thin, long, orange-yellow needles crystallize out. After filtration, these appear dark brown. They can be recrystallized from a large quantity of water, but the melting point of 183 °C remains unchanged. A yield of 315 mg (85 %) is obtained after drying over P_2O_5 *in vacuo*. Loss 4.8 %, reabsorption 4.8 %, calculated for 1 H_2O: 4.8 %.

The aldehyde betaines *(15)*, where n = 2, react very smoothly for a second time with a salt of type *(12)* containing the same or a different group R, to form symmetrical or unsymmetrical cyanines *(16)*. These are mostly blue-violet compounds, which are able to (de-) sensitize photographic emulsions. In compounds of type *(16)*, R and R′ may be either identical or different; *e.g.* either one may be *p*-bromophenyl, α-thienyl, *p*-biphenylyl, or β-naphthyl. The cyano [11] or the dithiomethoxycarbonyl group, S=C(SCH$_3$), [12] may replace the RCO group.



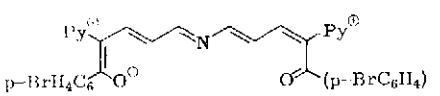
(16a) *(16b)*

Preparation of blue bis-pyridiniumcyanine betaine salts of type (16) [12a]

General procedure: Millimolar quantities of the components (salt *(12)* should be finely powdered) are suspended in 5 ml of acetic anhydride, the mixture is stirred vigorously, and 0.5 ml of pyridine is added. Almost immediately, the mixture becomes intensively blue (without the addition of pyridine, the reaction is considerably slower and requires higher temperatures). To obtain complete conversion, the mixture is heated at 80 °C for 5–10 minutes with good agitation. Because the dye-salt crystallizes out, the mixture occasionally acquires a pulpy consistency. The mixture is cooled, filtered, and washed, first with some cold acetic anhydride, and then with ether. Careful addition of ether to the filtrate yields an additional amount of product.

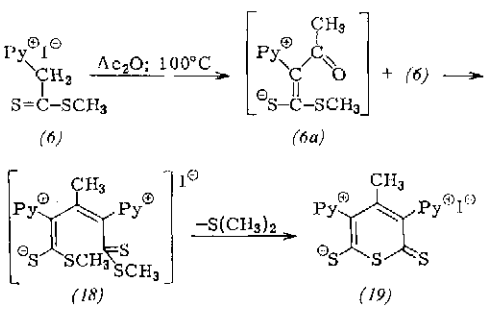
This procedure was used to prepare the bromide of 2,8-dipyridino-1-(*p*-bromophenyl)-9-methyl-1,3,5,7-nonatetraen-9-one-1-oxide *(16)*, where R = *p*-BrC$_6$H$_4$ and R′ = CH$_3$, starting from *(12)* with R = CH$_3$ and *(15)* with R = *p*-BrC$_6$H$_4$ and n = 2; the yield from 1 mmole of each component was 539 mg (97 %); the product crystallized from 250 parts of absolute ethanol plus 10 parts of absolute ether as clusters of blue needles, m.p. 187 °C (decomposition with effervescence). Loss and reabsorption 3.5 %; calculated for 1 H_2O: 3.3 %.

Methylanilinopropenal, OCHCH=CHN(CH$_3$)C$_6$H$_5$, which may also be regarded as a vinylogous formamide, reacts similarly to Zincke's aldehyde [13]. With *(12)*, compounds corresponding to the salts *(14)* to *(16)* but with two methine groups less and containing different R groups are obtained. These may be cyclized to give (3-pyridyl)pyridinium salts in the presence of glacial acetic acid and ammonium acetate [14]. Moreover, treatment of the aldehyde *(15)*, where n = 1, with dilute ammonia gives the blue-violet azabetaine cyanine *(17)* in 39 % yield.



(17)

Cyanines of type *(14)* and *(15)* with n = 0, or of type *(16)* [with one instead of five methine groups in the bridge] have not yet been prepared, since methylformanilide and formamide, for example, do not react with



(6) *(6a)* *(18)* *(19)*

[11] *A. Peuser*, Ph.D. thesis, Universität Gießen, 1962.

[12] *K. Gerlach*, Ph.D. thesis, Universität Gießen, 1960; *F. Kröhnke* and *K. Gerlach*, Chem. Ber. *95*, 1107 and 1110 (1962).

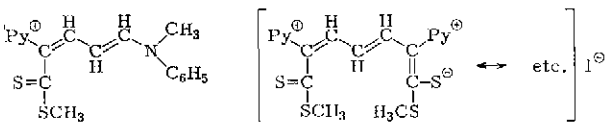
[12a] *K. Dickoré* and *F. Kröhnke*, Chem. Ber. *93*, 1073 (1960).

[13] *K. Dickoré* and *F. Kröhnke*, Chem. Ber. *93*, 2479 (1960).

[14] *F. Kröhnke* and *W. Zecher*, Angew. Chem. internat. Edit *1*, 626 (1962).

salts of type *(1)* [15]. However, a cyclic representative of the lower homologues of the cyanines *(19)* may be obtained by another route [16].

N-Dithiomethoxycarbonylmethylpyridinium iodide *(6)* reacts via its *C*-acetyl derivative *(6a)*, which is formed in hot acetic anhydride, to yield *(18)*. This cyanine corresponds in structure to type *(16)* but is methylated at the bridge methine group and cyclizes spontaneously to a thiopyran-α-thione *(19)* in 25 % yield with elimination of dimethyl sulfide. The salt *(6)* also reacts easily with methylanilinopropenal *(13)*, where n = 1: when pyridine is used as solvent, a carmine-red cyanine *(20)* separates out immediately at 20 °C in 92 % yield. Reaction of two moles of the iodide *(6)* with *(13)*, n = 1, at 80 °C yields the cyanine *(21)* at once, without intermediate hydrolysis [17].



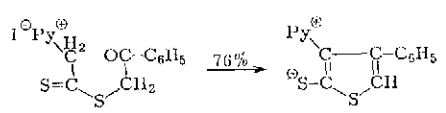
(20) *(21)*

Reaction of the salt *(6)* with *p*-dimethylaminobenzaldehyde yields a pyridinioethanol of type *(2)* even at 20 °C and without an alkaline catalyst [16]. This indicates that the methylene group in *(6)* is especially reactive, and thus, on treatment with nitrosodimethylaniline, this compound yields a nitrone in 66 % yield even without addition of alkali.

Cyanine formation in alcoholic solution is not achieved quite so easily; however, here the salt *(6)* reacts with Zincke's aldehyde more easily than with the propenal *(13)*, as is to be expected. This is so because with an increasing number of methine groups in the aldehyde, its polar resonance structure becomes richer in energy and therefore less important; consequently, there is an increase in the aldehyde character which is responsible for the success of the aldol reaction in alkaline-alcoholic solution.

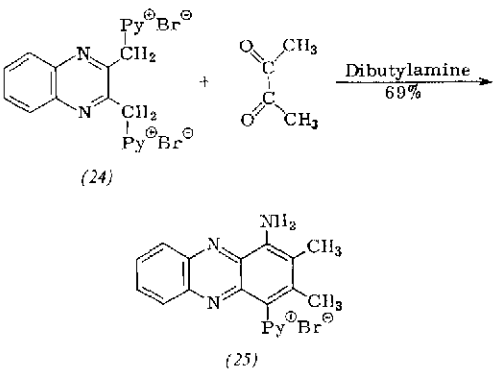
3. Phenazines from Quinoxalines and Alloxazines from Pteridines

Aldol condensation of *S*-phenacyl-dithiocarbonylmethylpyridinium iodide *(22)*, which corresponds structurally to salt *(6)*, with a ketonic compound was accomplished – actually by an intramolecular path [17] – and yielded the *N*-(2-mercapto-4-phenylthien-3-yl)pyridinium betaine *(23)*.



(22) *(23)*

The possibility of forming a five-membered ring as above, or a six-membered ring of aromatic character, undoubtedly favors the intramolecular aldol condensation, so that even a ketonic carbonyl group reacts with the *N*-methylenepyridinium group. This had already been shown by *Westphal* and *Jann* [18], who treated quinoxaline-2,3-bis-(*N*-methylenepyridinium bromide) *(24)* with diacetyl and obtained 1-amino-2,3-dimethyl-4-(*N*-pyridinio)phenazine bromide *(25)*:



(24)

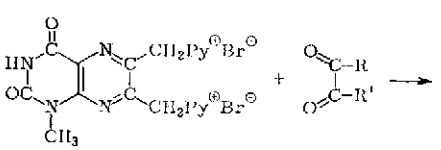
(25)

Preparation of 1-amino-2,3-dimethyl-4-(N-pyridinio)-phenazine bromide (25) [18]

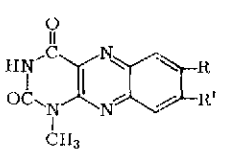
A mixture of 1 g of quinoxaline-2,3-bis-(*N*-methylenepyridinium) bromide *(24)* [18] and 0.7 g of diacetyl (theoretical 0.14 g) in 10 ml of ethanol is treated at 0 °C with 0.9 ml of dibutylamine. After standing for two days in the refrigerator, the mixture is filtered and washed thoroughly with alcohol/ether to give a yield of 570 mg (69 %). Recrystallization from 5 parts of water yields red needles of the very bitter tasting dihydrate, m.p. 304–305 °C.

When the catalyst is dibutylamine, then the C_5-chain of one of the pyridine rings is split off as above [19]. On the other hand, if the catalyst is piperidine, both pyridine rings remain intact [20], and 2,3-dimethyl-1,4-bis-(*N*-pyridinio)phenazine iodide is obtained. Finally, both pyridinium groups are split off on treatment with sodium ethoxide to yield 1,4-dihydroxy-2,3-dimethylphenazine [20], which crystallizes as red-brown needles.

Lately, *Henseke* and *Müller* [21] treated the bispyridiniopteridine derivative *(26)* with diacetyl to give the 1,6,7-trimethyl derivative *(27)* in 60 % yield, or with methylglyoxal to give 1,7-dimethylalloxazine *(28)* in 45 % yield.



(26)



(27) R = R' = CH_3
(28) R = H; R' = CH_3

[15] For additional data see *Kl. Gerlach*, Ph.D. thesis, Universität Gießen, 1960, pp. 35, 36.

[16] *F. Kröhnke*, *K. Gerlach*, and *K. E. Schnalke*, Chem. Ber. *95*, 1118 (1962).

[17] *F. Kröhnke* and *K. Gerlach*, Chem. Ber. *95*, 1107, 1110 (1962).

[18] *O. Westphal* and *K. Jann*, Liebigs Ann. Chem. *605*, 8 (1957).

[19] We describe this cleavage in Communication No. IV on "Syntheses Using Pyridinium Salts" which will appear shortly in Angew. Chem. internat. Edit.

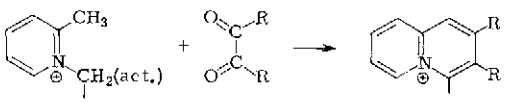
[20] *G. Henseke* and *Kl.-J. Bähner*, Chem. Ber. *91*, 1605 (1958).

[21] *G. Henseke* and *J. Müller*, Chem. Ber. *93*, 2668 (1960).

In the first case, a conversion from the quinoxaline to the phenazine series is obtained. The second reaction likewise proceeds via *ortho*-bis-pyridiniomethyl salts and therefore constitutes a preparatively useful route for conversions from the pteridine to the alloxazine series.

4. Syntheses of the Quinolizine Ring System and Related Types

A recent paper by *Westphal*, *Jann*, and *Heffe* [22] describes a highly comprehensive synthesis [23] of the quinolizine ring system, which is widespread among alkaloids. Thus, 2-picolinium salts with an activated *N*-pyridiniomethyl group *(29)* condense with 1,2-diketones in the presence of weakly basic agents such as dibutylamine or sodium bicarbonate to give 2,3-disubstituted dehydroquinolizinium salts *(30)* in good yields.

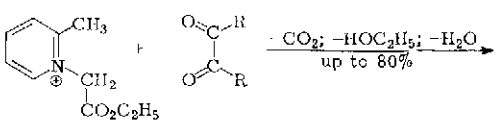


(29) (R = CH_3, C_6H_5 etc.) *(30)*

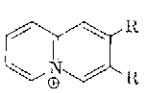
In alkaline solution, *N*-phenacyl-2-picolinium bromide *(31)*, which is suitable for the synthesis, tends to be transformed into 2-phenylpyrrocoline *(32)* [24]. This tendency can be suppressed by adding increasing amounts of 1,2-diketones, such as diacetyl, benzil, furil, or pyridil, the dehydroquinolizinium salt then being

(31) *(32)*

formed preferentially. By using *N*-ethoxycarbonylmethyl-2-picolinium bromide *(33)*, the formation of the pyrrocoline (indolizine) structure is completely eliminated, while the reactivity of the methylene group in ethoxycarbonylmethylpyridinium salts is still sufficient for condensation reactions [25a]; hence spontaneous hydrolysis of the ethoxycarbonyl group [25b, c] and decarboxylation generally occur, compound *(34)* being obtained.



(33) (R = CH_3, C_6H_5 etc.)



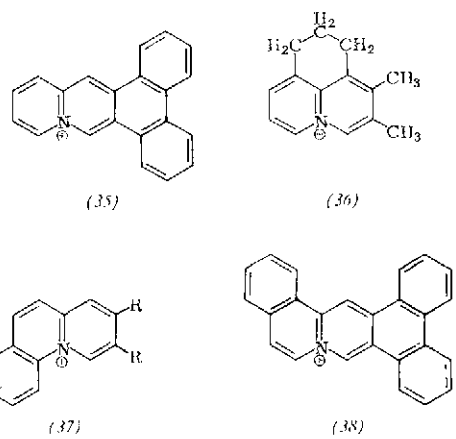
(34)

Preparation of 2,3-dimethyldehydroquinolizinium bromide, i.e. the bromide of (34), where R = CH_3 [22].

Dibutylamine (1.29 g) is added to a solution of 2.5 g of *N*-(ethoxycarbonylmethyl)-2-picolinium bromide *(33)* [22] and 0.9 g of diacetyl in 20 ml of ethanol, and the mixture is refluxed 40 minutes. It is then evaporated to dryness *in vacuo*, the residue is washed with ether and acetone and recrystallized from ethanol/ether to yield 1.8 g (70 %) of colorless cubes, m.p. 233 °C.

With phenanthroquinone, 2,3,9′,10′-phenanthrodehydroquinolizinium bromide *(35)* is obtained. The 2-ethylpyridinium and the 2,6-lutidinium salts yield 1- and 6-methyldehydroquinolizinium salts, respectively; other positions of the pyridine ring may also be substituted. Thus 1,9-trimethylene-2,3-dimethylquinolizinium bromide *(36)* is prepared from *N*-(ethoxycarbonylmethyl)-5,6,7,8-tetrahydroquinolinium bromide and diacetyl.

Appropriate quinaldinium and 1-methylisoquinolinium or 1-methyl-3,4-dihydroisoquinolinium salts also react. One such product from a reaction of a quinaldinium salt is *(37)*. The system of six fused rings of 2,3,9′,10′-phenanthro-8,9-benzodehydroquinolizinium bromide *(38)* is obtained in 40 % yield from *N*-(ethoxycarbonylmethyl)-1-methylisoquinolinium bromide and phenanthroquinone.



(35) *(36)* *(37)* *(38)*

The application of this very elegant synthesis is somewhat restricted by the fact that, in salts of type *(29)*, an especially active *N*-methylene group decreases the reactivity of the α-methyl group because it favors formation of a methylene base [25d].

The reaction of 2-acylpyridines with α-bromoketones in acetonitrile yields *N*-(acylmethyl)-2-acylpyridinium salts *(39)*. On treatment with alkali followed by mineral acid, the latter yield substituted 1-hydroxydehydroquinolizinium salts *(40)* via phenol betains; however, when heated with ammonium acetate/glacial acetic acid, they are converted into 2-azadehydroquinolizinium salts *(41)*, whereas with a 25 % hydrazine hydrate solution, they give 1,2-disubstituted indolizines *(42)* [25e].

Schraufstätter [25f] recently described a route, similar to that leading to *(40)*, which yielded 3-hydroxyde-

[22] *O. Westphal*, *K. Jann*, and *W. Heffe*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *294*, 37 (1961).

[23] German Patent Application W. 25798 IV b/12 p (June 11th, 1959).

[24] *A. E. Tschitschibabin*, Ber. dtsch. chem. Ges. *60*, 1607 (1927).

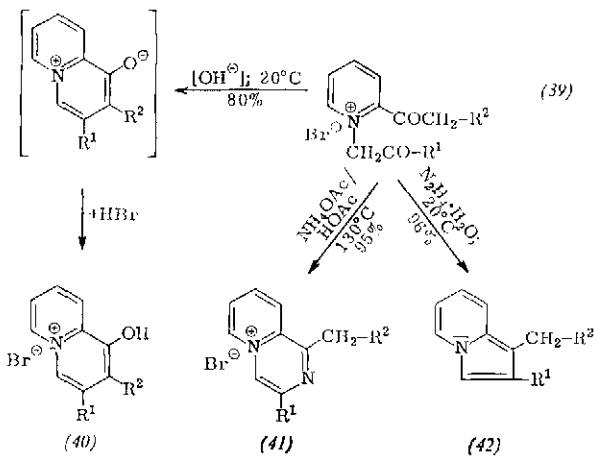
[25] [a] *F. Kröhnke*, Ber. dtsch. chem. Ges. *70*, 546 (1937); [b] *ibid. 73*, 310 (1940); [c] *E. D. Bergmann*, *H. Bendas*, and *Ch. Resnick*, J. chem. Soc. (London) *1953*, 2564, 2568.

[25d] *I. Naményi*, Diploma thesis, Universität Gießen, 1962, and Ph. D. thesis, 1963 (in preparation).

[25e] Taken from the Ph. D. thesis of *W. Weis*, Universität Gießen, 1963; many additional examples are given there.

[25f] *E. Schraufstätter*, Angew. Chem. internat. Edit. *1*, 593 (1962).

hydroquinolizinium bromide starting from the diethyl acetal of pyridine-2-carboxaldehyde and proceeding via the *N*-acetonylpyridinium salt.

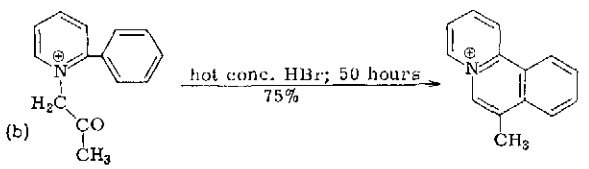


(39)

(40) (41) (42)

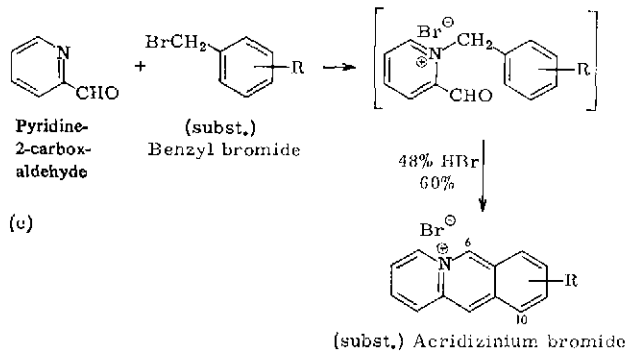
(The yields given refer to the substitutents $R^1 = C_6H_5$, $R^2 = H$).

Several years ago, *Bradsher* and coworkers [26] synthetized the (benzo-)dehydroquinolizinium system from pyridinium salts by routes (b) and (c) [27].



N-Acetonyl-α-phenylpyridinium halide

7-Methylbenzo[a]dehydroquinolizinium bromide



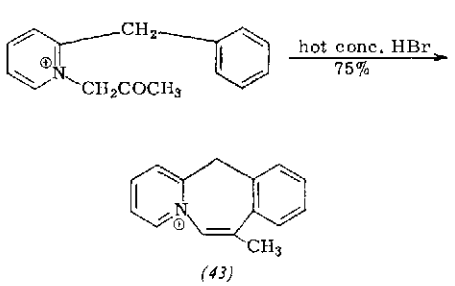
Pyridine-2-carboxaldehyde

(subst.) Benzyl bromide

(c)

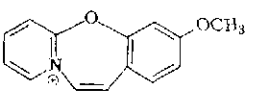
(subst.) Acridizinium bromide

The synthesis of the morphanthridizinium sekeleton *(43)* was likewise accomplished by treating *N*-acetonyl-2-benzylpyridinium halide with hot concentrated hydrobromic acid [28].



(43)

Appropriately substituted *N*-acetonyl-2-phenoxypyridinium bromides undergo very smooth ring closure to form the pyrido[2,1-*b*]benz[*f*]-1,3-oxazepinium system *(43a)* [29].

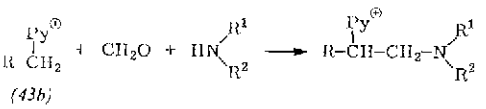


(43a)

Winterfeld and *Buschbeck* [29a] achieved the synthesis of the quinolizidine and 2-oxaquinolizidine systems in two steps, starting from 2-acetylpyridine, and of the 1,3-dioxoquinolizidine system in three steps, starting from an α-picolinic ester.

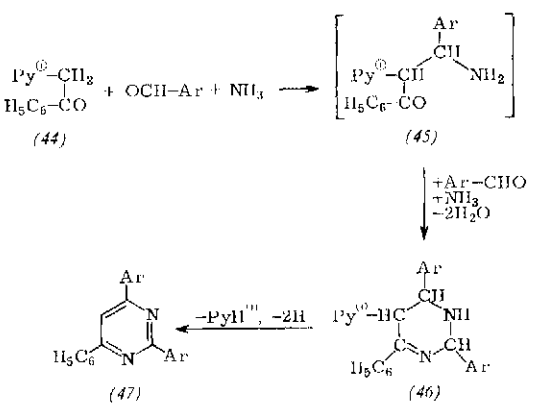
II. Mannich Reactions and Aminoalkylations

The only example known of Mannich reaction of a pyridinium salt *(43b)* containing an active *N*-methylene



(43b)

group is that involved in a recently discovered new pyrimidine synthesis [30], where a Mannich condensation is the crucial step. There, *N*-phenacylpyridinium bromide *(44)* reacts in glacial acetic acid with ammonia or ammonium acetate and a benzaldehyde containing a substituent with a (−I)-effect; evidently the reaction first proceeds via a Mannich-type reaction to give ω-aminopropiophenone *(45)*, which then reacts with the ammonia and the substituted benzaldehyde and cyclizes to the 2,3,4,5-tetrahydropyrimidine *(46)*. The latter pyrolyzes smoothly to a dihydropyrimidine which is then



(44) (45) (47) (46)

[26] *C. K. Bradsher* and *L. E. Beavers*, J. Amer. chem. Soc. *77*, 453 (1955) and numerous later papers by *Bradsher*, the last one in J. org. Chemistry *26*, 2231 (1961).

[27] *C. K. Bradsher* and *L. E. Beavers*, J. Amer. chem. Soc. *77*, 4812 (1955). The name "acridizinium" has been proposed there.

[28] *K. B. Moser* and *C. K. Bradsher*, J. Amer. chem. Soc. *81*, 2547 (1959) and later papers, the last one: *C. K. Bradsher*, *L. D. Quin*, and *R. E. Le Bleu*, J. org. Chemistry *26*, 3278 (1961): Synthesis of the isomorphanthridizinium system from *N*-benzyl-2-acetonylpyridinium bromide in 20–30% yield.

[29] *C. K. Bradsher*, *L. D. Quin*, and *R. E. Le Bleu*, J. org. Chemistry *26*, 3273 (1961).

[29a] *K. Winterfeld* and *H. Buschbeck*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *294*, 468 (1962).

[30] *E. Schmidt*, Ph. D. thesis, Universität Gießen, 1962; *F. Kröhnke*, *E. Schmidt*, and *W. Zecher*, Chem. Ber., in the press.

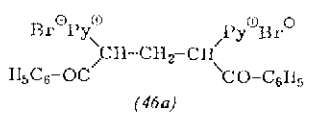
dehydrogenated very conveniently by the excess substituted benzaldehyde present to give the triarylpyrimidine *(47)* in 57–84 % yield.

Other salts may also be used in this pyrimidine synthesis instead of *(44)*. For example, the reaction between phenacyldimethylsulfonium bromide and *p*-nitrobenzaldehyde gives the pyrimidine derivative in 80 % yield; phenacylisoquinolinium bromide reacts less favorably (45 % yield), and phenacylquinolinium bromide reacts poorly (5 % yield). Acetonylpyridinium bromide yields a 2,4-diaryl-6-methylpyrimidine, and the methyl group of the latter immediately reacts further with the aromatic aldehyde to give a styryl group.

Preparation of 2,4-bis-(p-nitrophenyl)-6-phenylpyrimidine [31]

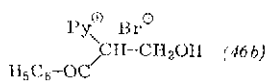
A solution of 2.78 g (10 mmoles) of phenacylpyridinium bromide *(44)* and 3.78 g (25 mmoles) of *p*-nitrobenzaldehyde in 8 ml of glacial acetic acid containing 6 g of ammonium acetate is refluxed for 1.5 hours. The reaction mixture is then boiled with 6 ml of methanol to yield a red-brown semisolid crystalline mixture, which is filtered off and washed with methanol and hot water to yield 3.1 g (76.5 %) of crystals. Recrystallization from dimethylformamide (avoiding prolonged heating!) yields dirty yellow, small, lance-shaped crystals, m.p. 293–294 °C.

On the other hand, methylene-bis(phenacylpyridinium) bromide *(46a)* [32] was always formed on treating phenacylpyridinium bromide *(44)* with formaldehyde and piperidine under various reaction conditions. Formaldehyde reacts very readily with *(44)*; the methyl compound *(46b)* first formed can be isolated and proves to



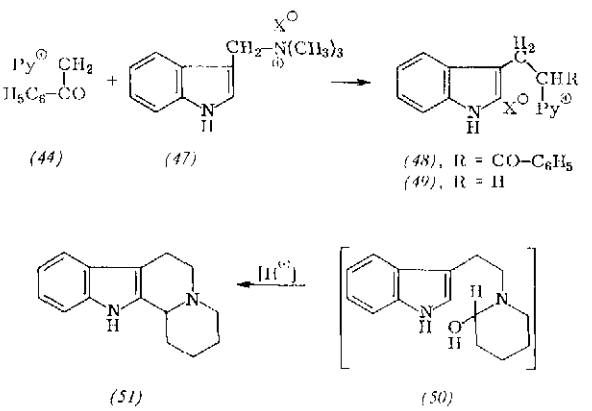
(46a)

be more reactive towards a second mole of *(44)* than towards the secondary base, and consequently no Mannich base is formed.



(46b)

Thesing [33] has shown that pyridinium salts of type *(44)* may be alkylated at the reactive methylene group with quaternary salts of gramine. Thus, the gramine salt *(47)* reacts with *(44)* at 20 °C to yield the alkylation product *(48)*, which undergoes "acid hydrolysis" under the alkaline experimental conditions to give *(49)*. *N*-(β-Indolylethyl)pyridinium salts of type *(49)* are thus obtained conveniently in almost quantitative yields. On partial hydrogenation of the pyridinium ring according to *Schöpf* [34], the aldehyde-ammonia *(50)* is formed and is converted in weakly acid solution into indoloquinolizine *(51)*. Compound *(50)* itself was not isolated.

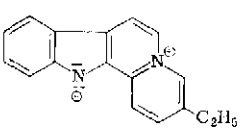


(44) *(47)* *(48)*, R = CO–C$_6$H$_5$; *(49)*, R = H

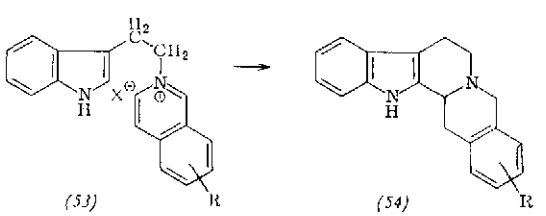
(51) *(50)*

By using *N*-phenacyl-β-ethylpyridinium bromide instead of *(44)*, *Thesing* and *Festag* [35] achieved a synthesis of the indole alkaloid flavopereirine *(52)* via steps analogous to the sequence *(48)* → *(49)* → *(50)* → *(51)*; compound *(52)* was finally obtained on dehydrogenation of the compound corresponding to *(51)* with palladium.

If an *N*-phenacylisoquinolinium salt substituted in the isoquinoline ring is used instead of the salt *(44)* [36], then the *N*-(β-indol-3-ylethyl)isoquinolinium salt *(53)* is obtained in place of *(49)*. Compound *(53)* may be condensed by a sequence of reactions analogous to *(49)* → *(50)* → *(51)* to yield the indolo[2,3-*a*]quinolizine derivative *(54)*, which possesses the basic skeleton of yohimbine or reserpine.



(52)



(53) *(54)*

III. The Ortoleva-King-Reaction

According to *King* [37], pyridinium salts can often be conveniently and advantageously prepared in a direct synthesis by heating active methyl and methylene compounds with iodine in pyridine:

$$\rangle CH_2 + I_2 + 2\ NC_5H_5 \rightarrow \rangle CH\text{–}Py^{\oplus}\ I^{\ominus} + NC_5H_5 \cdot HI$$

[31] *E. Schmidt*, Ph. D. thesis, Universität Gießen, 1962, p. 104.

[32] *J. Curtze*, Diploma thesis, Universität Gießen, 1961. Acetoacetates and other β-ketoesters (which are also similar to phenacylpyridinium salts in other respects) behave similarly towards amines + formaldehyde: only methylenebis(acetoacetates) and corresponding derivatives of the other β-ketoesters are obtained: *E. Knoevenagel*, Liebigs Ann. Chem. *281*, 25 (1894). On the other hand, α-alkylacetoacetates are obtained in good yield by the Mannich reaction: *K. Bodendorf*, *K. J. Krüger*, and *F. Zernial*, Liebigs Ann. Chem. *562*, 1 (1949).

[33] *J. Thesing*, *H. Ramloch*, *C. Willersinn*, and *F. Funck*, Angew. Chem. *68*, 387 (1956).

[34] *C. Schöpf*, *G. Herbert*, *R. Rausch*, and *G. Schröder*, Angew. Chem. *69*, 391 (1957).

[35] *J. Thesing* and *W. Festag*, Experientia *15*, 127 (1959); for a synthesis of flavopereirine by another route see *E. Wenkert* and *J. Kilzer*, J. org. Chemistry *27*, 2283 (1962).

[36] *J. Thesing*, German Published Patent Application 1111634 (Nov. 23rd, 1956/July 27th, 1961); US-Pat. 2891955.

[37] *L. C. King*, J. Amer. chem. Soc. *66*, 894 (1944) and many later papers. See also *F. Krähnke*, Angew. Chem. *65*, 608 (1953), top of left column.

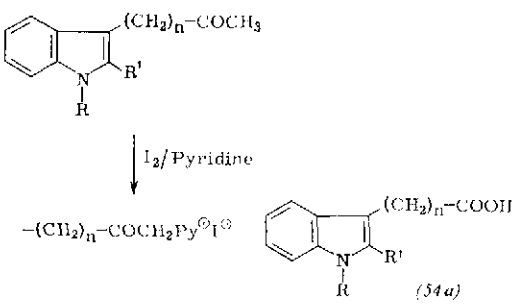
The pyridine also serves as solvent and is therefore used in considerable excess. The yields in this elegant method are usually very good and often (but not always) surpass those of the two-step procedure. The separation of the mixture of iodides formed is sometimes accompanied by considerable losses, but this can be circumvented, according to *Ried* [38], by precipitating the product from the aqueous solution with sodium perchlorate; the pyridine is not coprecipitated.

In the meantime it has been discovered that *Ortoleva* [39] had been the first to recognize the possibility of this synthesis of pyridinium salts a long time ago:

$$(HOOC)_2CH_2 + I_2 + 2\,NC_5H_5 \xrightarrow{-CO_2} HOOC{-}CH_2{-}Py^{\oplus}\,I^{\ominus} + NC_5H_5{\cdot}HI$$

We therefore designate this very useful procedure as the "Ortoleva-King reaction," since *King* was obviously the first to recognize its preparative significance.

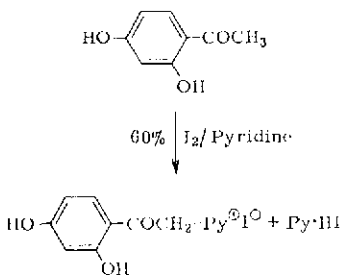
Meanwhile, this method has been applied in numerous fields and was recently used in the field of indole chemistry to prepare substituted indole- and *N*-methylindole-3-carboxylic acids and -3-propionic acids *(54a)* [40].



(54a)

(R = R' = H or CH_3; n = 0 or 2)

The preparation of phenacylpyridinium salts which are substituted in the phenyl ring with hydroxyl, methoxyl, or other groups [41, 42] (and which are therefore easily brominated in the benzene ring) is especially convenient and, in fact, often succeeds only by using the above method. This method is also useful with α-tetralone [37], and naphthyl or anthryl methyl ketone. An example is given in reaction (d).



[38] *W. Ried* and *H. Bender*, Chem. Ber. *89*, 1893 (1956).

[39] *G. Ortoleva*, Gazz. chim. ital. *29* I, 503 (1899); Chem. Zbl. *1900* I, 1013; Gazz. chim. ital. *30* I, 509 (1900); Chem. Zbl. *1900* II, 315.

[40] *G. Hart* and *K. T. Potts*, J. org. Chemistry *27*, 2940 (1962).

[41] *L. C. King*, *M. Mc. Whirter*, and *D. M. Barton*, J. Amer. chem. Soc. *67*, 2089 (1945).

[42] *J. L. Hartwell* and *S. R. L. Kornberg*, J. Amer. chem. Soc. *68*, 868 (1946).

Benzyl styryl ketone *(55)* is also converted into the pyridinium salt, the double bond remaining intact [43].

$$\underset{(55)}{Ph{-}CH{=}CH{-}CO{-}CH_2{-}Ph} \xrightarrow{I_2/Pyridine} Ph{-}CH{=}CH{-}CO{-}CH_2{-}Py^{\oplus}\,I^{\ominus} + Py{\cdot}HI$$

Other heterocyclic bases may be used instead of pyridine, for example, picolines, quinolines, isoquinolines, and nicotinamide [44], as well as thiourea [45] and dimethyl sulfoxide [46]. If the reaction can be carried out at room temperature, the iodine may occasionally be replaced by bromine; however, this is seldom advantageous [47, 48]. Pyridine perhalide may also be used [49].

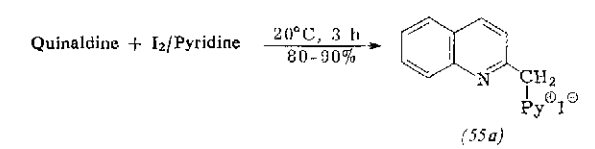
Other compounds containing active methyl and methylene groups may be substituted for the methyl and methylene ketones in the reaction. These include *N*-methyl-α- [49] and -γ-picolinium iodide [50], α- and γ-methyl derivatives of benzothiazoles and benzoxazoles, pyrimidines and pyrazines [51], quinaldine, lepidine [52, 53], and 9-methylacridine [53], as well as acetylpyridines, acetone, 2,4-dinitrotoluene, phenacyl thioethers [53a], and 2-methyl-γ-chromone [54].

Preparation of phenacylisoquinolinium iodide [42, 44]

$$PhCOCH_3 + I_2 + 2\,NC_9H_7(iso) \xrightarrow[95\,\%]{} [PhCOCH_2{-}NC_9H_7]^{\oplus}I^{\ominus} + NC_9H_7{\cdot}HI$$

A solution of 0.1 mole of acetophenone in 30 g of isoquinoline is treated with 0.1 mole of iodine. The mixture is heated overnight on a water bath, cooled, and washed thoroughly with ether. The yield is 3.56 g (95 %). Recrystallization from acetone/alcohol yields yellow prisms, m.p. 178–180 °C.

The *N*-(2-quinolylmethyl)pyridinium iodide *(55a)* [52, 53] is obtained in a similar manner.



(55a)

[43] *D. I. Sapper* and *P. L. Southwick*, J. org. Chemistry *21*, 105 (1956).

[44] *L. C. King* and *M. Mc. Whirter*, J. Amer. chem. Soc. *68*, 717 (1946).

[45] *R. M. Dodson* and *L. C. King*, J. Amer. chem. Soc. *67*, 2242 (1945); *68*, 871 (1946). In these papers, bromine, chlorine, or other oxidizing agents are also used instead of iodine; *E. Fournier* and *L. Petit*, C. R. hebd. Séances Acad. Sci. *252*, 291 (1961).

[46] *F. Kröhnke*, *K. F. Gross*, and *H. Schäfer*, unpublished results.

[47] *W. H. Stafford*, J. chem. Soc. (London) *1952*, 581 (Indane-1,3-dione).

[48] *F. Kröhnke* and *K. F. Gross*, Chem. Ber. *92*, 22 (1959), (Quinaldine).

[49] *J. A. Berson* and *Th. Cohen*, J. Amer. chem. Soc. *78*, 416 (1956).

[50] *F. Kröhnke*, *H. Leister*, and *I. Vogt*, Chem. Ber. *90*, 2792 (1957).

[51] *W. Ried* and *R. M. Gross*, Chem. Ber. *90*, 2646 (1957).

[52] *L. C. King* and *S. V. Abramo*, J. org. Chemistry *23*, 1609 (1958).

[53] *L. C. King* and *S. V. Abramo*, J. org. Chemistry *23*, 1926 (1958).

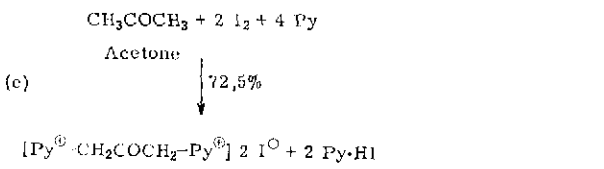
[53a] *F. Kröhnke* and *K. F. Gross*, Chem. Ber. *92*, 28 (1959).

[54] *J. Schmutz*, *R. Hirt*, and *H. Lauener*, Helv. chim. Acta *35*, 1168 (1952).

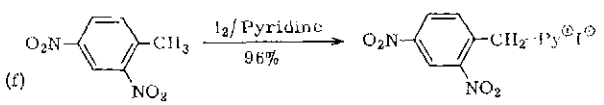
The advantages of the procedure are especially evident here, since it is difficult to monobrominate quinaldine. Bromination proceeds easily to the di- and tribromo compounds, even when less than one equivalent of bromine is used [55].

9-Methylacridine also reacts within a few minutes with a solution of iodine/pyridine even at room temperature or on warming to give *N*-(acrid-9-ylmethyl)pyridinium iodide [48]. The reactions of 1-methylisoquinoline [52], lepidine [52], and 2,6-dimethylquinoline [52] are similar. On the other hand, α-, γ-, and especially β-picoline do not undergo the Ortoleva-King reaction [48]; however, α- and γ-picoline-*N*-oxides [56] do give this reaction since the reactivity of their methyl group is intermediate between that of the picolines and that of the picolinium salts.

The reactions of acetone and 2,4-dinitrotoluene are further examples [equations (e) and (f)].



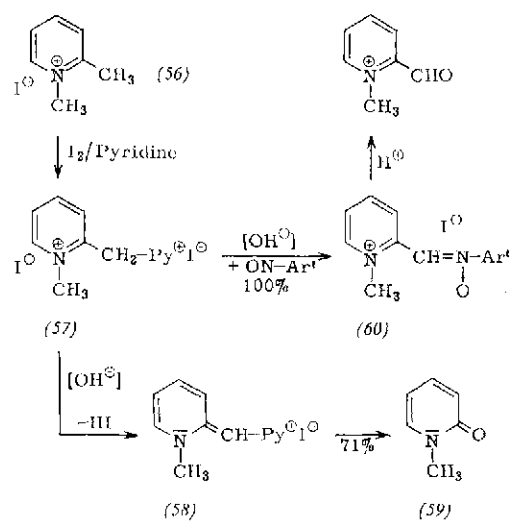
Acetonylene-bis(pyridinium) iodide [48]



2,4-Dinitrotoluene

1-(2,4-Dinitrobenzyl)-pyridinium iodide [48]

The Ortoleva-King reaction may be followed by further reactions, sometimes without isolating the primary product [56a]; occasionally these reactions occur spontaneously. This is shown in the following examples.

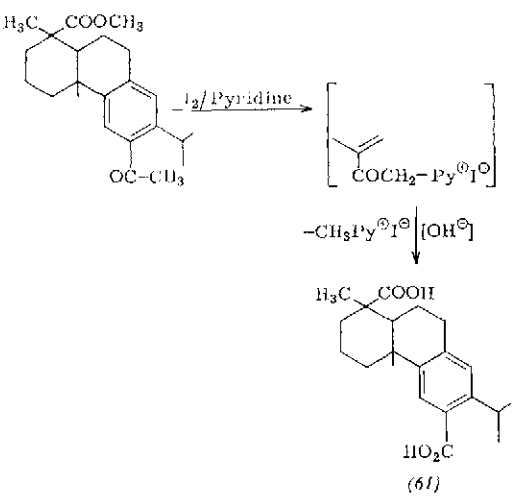


Thus, in dilute sodium hydroxide, *N*-(1-methyl-2-pyridiniomethyl)pyridinium diiodide *(57)* [57], which is obtained from *N*-methyl-α-picolinium iodide *(56)*, reacts with water to yield *N*-methyl-2-pyridone *(59)*. The reaction proceeds even at 20 °C. The assumption that the blood-red intermediate which appears during the reaction possesses structure *(58)* [58] has been verified in the meantime [59]. This synthesis of 2-pyridones according to *Berson* and *Cohen* has occasionally been used [60, 61].

Preparation of N-methyl-2-pyridone from the diiodide (57) [57]

Treatment of a solution of 1.08 g of *(57)* in 5 ml of water with 0.6 N sodium hydroxide gives a blood-red color [due to *(58)*], which disappears within a few seconds. More alkali is added (the total being 20 ml) until no further color appears. The light yellow solution is then extracted several times with chloroform and the extract dried with potassium carbonate to yield 0.19 g (71 %) of compound *(59)* as a pale yellow oil; m.p. of picrate: 140.5–142.2 °C. *N*-Methylpyridinium-2-carboxaldehyde iodide was also prepared from the diiodide *(57)* but was isolated only as the nitrone *(60)* [58].

The well known "acid hydrolysis" of the phenacylpyridinium salts [62] can also be directly coupled to the Ortoleva-King reaction without isolating the pyridinium salt. Thus, *Pratt* [63] obtained 6-carboxydehydroabietic acid *(61)* in 70–80 % yield starting from methyl 6-acetyldehydroabietate and proceeding via the pyridinium salt prepared according to King which was, however, not isolated.



After removal of the pyridine *in vacuo*, the residue was dried at 130 °C and then heated with 1 N potassium hydroxide in diethyleneglycol (containing a trace of water), whereby the pyridinium salt underwent acid hydrolysis [62].

Equations (g)–(k) show that the Ortoleva-King reaction may often be followed by extremely easy ring closures to yield other heterocycles.

[55] *D. L. Hammick*, J. chem. Soc. (London) *1923*, 2882; *1926*, 1302; and later papers, *ibid.* up to 1957.

[56] *B. Umezawa*, Chem. pharmac. Bulletin (Tokyo) *8*, 698 (1960).

[56a] See fourth communication in this series: *F. Kröhnke*, Angew. Chem. internat. Edit. *2* (1963), in the press, Section II.

[57] *J. A. Berson* and *Th. Cohen*, see [49].

[58] *F. Kröhnke*, *H. Leister* u. *I. Vogt*, Chem. Ber. *90*, 2794 (1957).

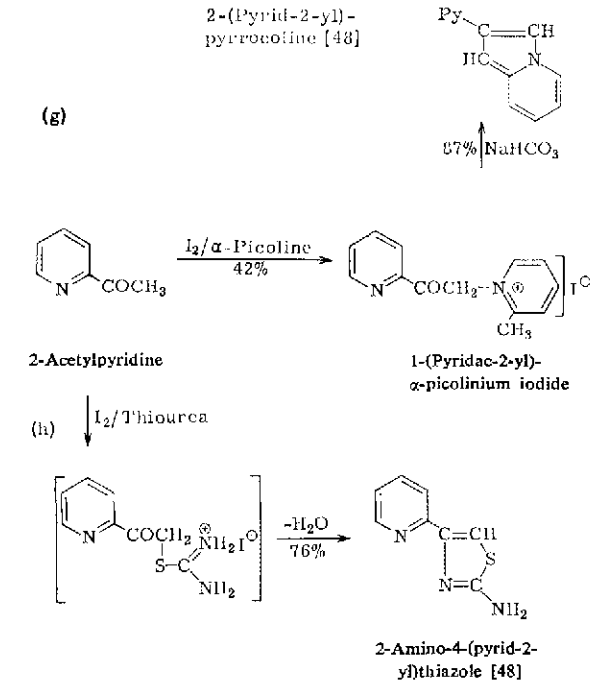
[59] *H. Leister*, Ph. D. thesis, Universität Gießen, 1958, pp. 53, 78.

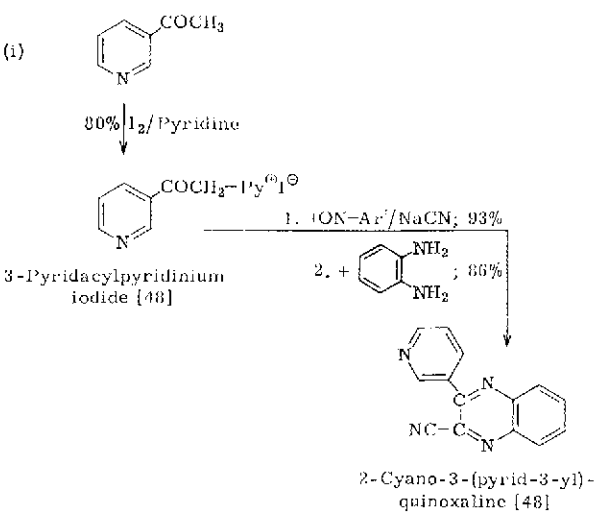
[60] *F. Kröhnke* and *K. F. Gross*, Chem. Ber. *92*, 25 (1959).

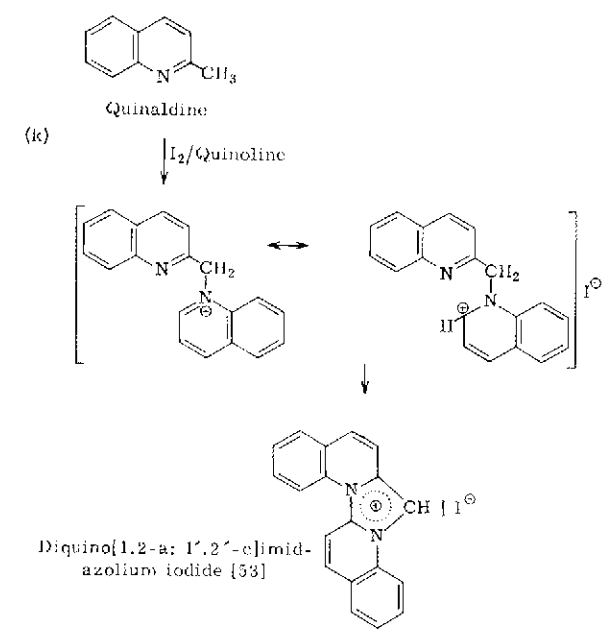
[61] *A. R. Battersby* and *J. C. Turner*, J. chem. Soc. (London) *1960*, 717; *B. Umezawa*, Chem. pharmac. Bulletin (Tokyo) *8*, 918 (1960); further data on the pyridone synthesis are to be found therein.

[62] Cf. *F. Kröhnke*, Angew. Chem. *65*, 607 (1953).

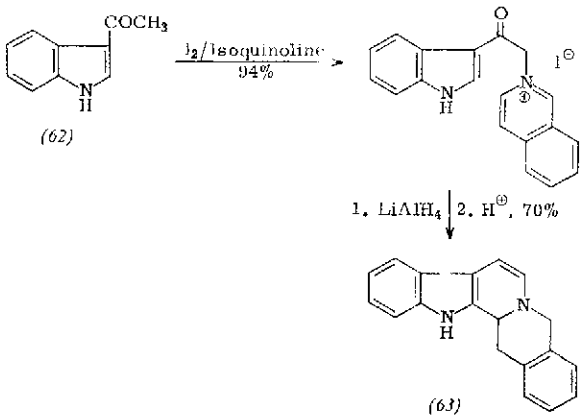
[63] *Y. T. Pratt*, J. Amer. chem. Soc. *73*, 3803 (1951).



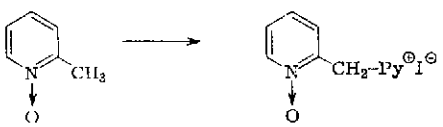




The Ortoleva-King reaction has found application in an elegant two-step synthesis of the yohimbine skeleton *(63)* starting from 3-acetylindole *(62)* [64].



2-Picoline-*N*-oxide *(64)* also undergoes this reaction [65].



(64) *(65)* 1-(1-Oxidopyrid-2-ylmethyl)-pyridinium iodide

For the conversion of Ortoleva-King products via the nitrones or the "red anils" into aldehydes and α-keto-carboxylic acids see [66].

King and *Miller* [67] treated diazoketones with salts of heterocyclic amines in similar manner and obtained *N*-phenacylpyridinium salts *(66)*. Just like active methyl

$$PhCOCH_2N_2 + Py^{\oplus}\,ClO_4^{\ominus} \xrightarrow[93\,\%]{-N_2} PhCOCH_2{-}Py^{\oplus}\,ClO_4^{\ominus}$$

(66)

groups, primary (and secondary?) alcoholic groups may also be converted directly into *N*-methylenepyridinium salts [68] (variant introduced by *Karrer* [69]).

$$-CH_2OH \xrightarrow{p\text{-toluenesulfonylchloride/pyridine}} [-CH_2Cl] \rightarrow -CH_2Py^{\oplus}\,Cl^{\ominus}$$

Basically, the Ortoleva-King reaction succeeds not only with pyridine, *etc.* but also at the oxygen of pyridine-*N*-oxide *(67)*. Any methyl or methylene group is converted hereby into –CHO and C=O, respectively [70] [compare the reaction *(64)* → *(65)*].

[64] *D. R. Liljegren* and *K. T. Potts*, Proc. chem. Soc. (London) *10*, 340 (1960).

[65] *M. Hamana, B. Umezawa, Y. Gotoh*, and *K. Noda*, Chem. pharmac. Bulletin (Tokyo) *8*, 692 (1960).

[65a] *W. Schulze*, J. prakt. Chem. (4) *19*, 94 (1963).

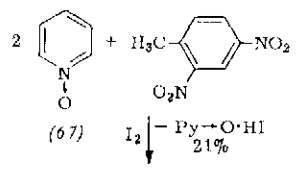
[66] Communication No. IV on "Syntheses Using Pyridinium Salts": *F. Kröhnke*, Angew. Chem. internat. Edit. *2* (1963), in the press, Section II.

[67] *L. C. King* and *F. M. Miller*, J. Amer. chem. Soc. *70*, 4154 (1948).

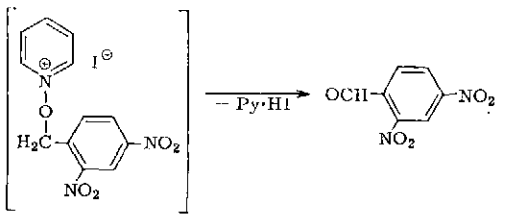
[68] *W. J. Leanza, J. B. Conbere, E. F. Rogers, K. Pfister III*, J. Amer. chem. Soc. *76*, 1691 (1954): Cortisone → Cortisone-21-pyridinium chloride or tosylate.

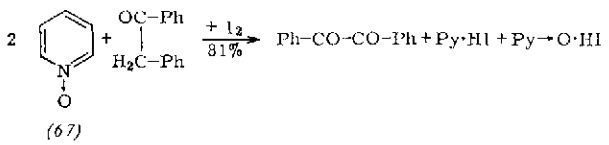
[69] *P. Karrer* and *A. Epprecht*, Helv. chim. Acta *24*, 1039 (1941).

[70] *H. Schäfer*, Ph. D. thesis, Universität Gießen, 1960, pp. 38, 67.



(67)



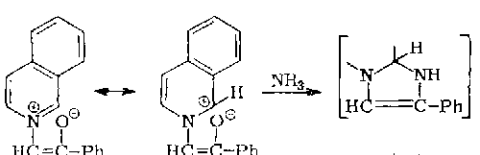


(67)

IV. Cycloimmonium Salts and Amines with Active N-Methylene Groups

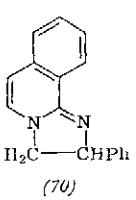
1. Aliphatic Amines and Hydrazine

The α-positions in quinolinium and isoquinolinum salts containing active *N*-methylene groups are considerably more activated than those in pyridinium salts. Specifically, in the case of phenacylisoquinolinium betaine, an inactive form was isolated besides the active "enol betaine"; its behavior accords best with formula *(68)* [71]. Its reaction with ammonia or ammonium acetate/glacial acetic acid proceeds via the partial structure *(69)* to give essentially 2,3-dihydroimidazoisoquinoline *(70)* in 70 % yield. Similarly, 2-phenyl-1,2-dihydroimidazo-[1,2-*a*]quinoline *(71)* is formed in the quinolinium series [71].



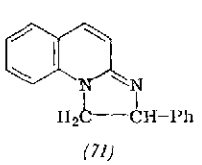
(68)

(69)

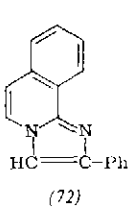


(70)

Hydroxylamine reacts like ammonia here: in the isoquinolinium series, it gives the dehydro product *(72)*, *i.e.* 2-phenylimidazo[2,1-*a*]isoquinoline, in 75 % yield. This reaction is even more successful in the quinolinium series, where it gives an 85 % yield of 2-phenylimidazo-[1,2-*a*]quinoline [71].

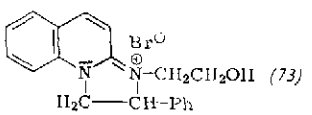


(71)



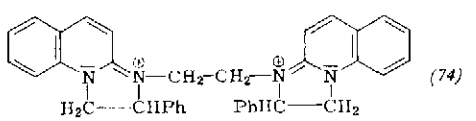
(72)

It was then found that aliphatic amines behave like ammonia, betaines of the quinolinium series again reacting appreciably more readily than those of the isoquinolinium series. On the other hand, betaines of the pyridinium series do not react at all or react in a manner that is not yet fully understood. Thus, for example, reaction of ethanolamine and phenacylquinolinium bromide in glacial acetic acid yields the quaternary salt *(73)* in 94 % yield.

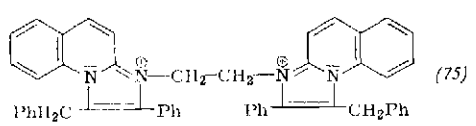


(73)

Aliphatic diamines always form the bis-compounds even when they are present in large excess. Thus, ethylenediamine reacts with phenacylquinolinium bromide in glacial acetic acid to yield ethylene-3,3'-bis-(2-phenyl-1,2-dihydromidazo[1,2-*a*]quinolinium) bromide *(74)* [72].



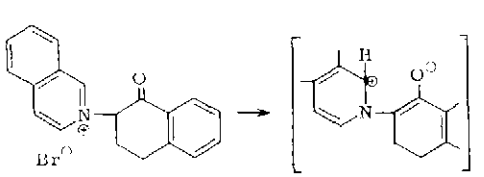
(74)



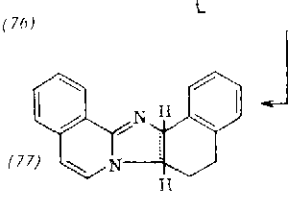
(75)

The reaction with benzaldehyde results in aromatization of the imidazole ring [→ *(75)*] via migration of the initially exocyclic double bond, an effect which cannot be accomplished by dehydrogenation [72].

Derivatives of the naphtho[1'2':4,5]imidazo[2,1-*a*]isoquinoline system *(77)* may be easily obtained by treatment of *N*-(α-tetralonyl)isoquinolinium bromide *(76)* with ammonia or amines [72]. This ring system was already obtained in small yield by another route by *Morgan* and *Stuart* [73]. If hydroxylamine is used instead of



(76)



(77)

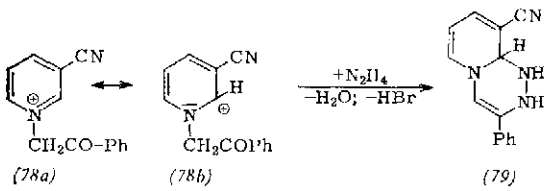
[71] *F. Kröhnke* and *W. Zecher*, Chem. Ber. *95*, 1128 (1962).

[72] *K. Osterheld*, Ph.D. thesis, Universität Gießen, 1963.

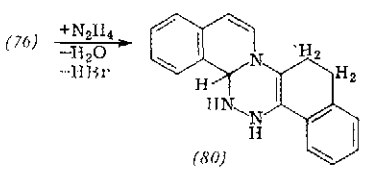
[73] *G. Morgan* and *J. Stuart*, J. chem. Soc. (London) *1939*, 1057.

ammonia, then the dehydro derivative of *(77)* is obtained (indicated in the formula by the dotted line).

Interesting reactions are also possible with hydrazine. However, the reaction of phenacylpyridinium bromide with hydrazine does not lead to a ring closure. On the other hand, the α-position of the pyridinium ring of the 3-cyano-*N*-phenacylpyridinium bromide *(78a, b)* is as strongly positive as that in the (iso)quinolinium cation [74]. Hydrazine therefore readily yields the pyridinotriazine *(79)*.



(78a) *(78b)* *(79)*

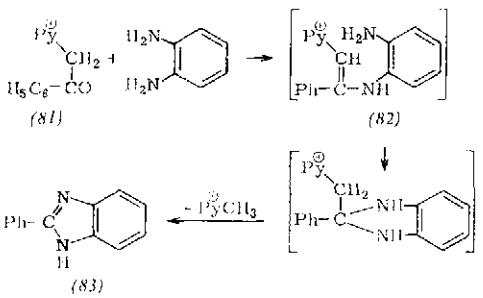


(80)

We have reported elsewhere [72] on an anomalous reaction of phenacylisoquinolinium bromide leading to 2,5-diphenylpyrazine. In contrast, on reaction with hydrazine in warm alcohol, *N*-tetralonylisoquinolinium bromide *(76)* leads smoothly to the expected triazine derivative *(80)* [72]. Here the analogous 3-cyanopyridinium derivative also behaves like the isoquinolinium salt *(76)* and not like the unsubstituted pyridinium salt. The resulting ring system, as well as that of *(79)* and *(80)* was probably hitherto unknown.

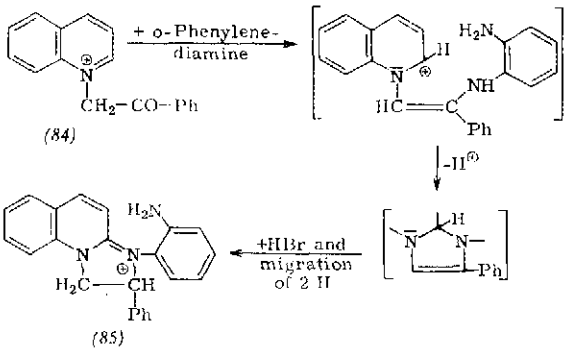
2. Aromatic Primary Amines and *o*-Phenylenediamine

Reaction of phenacylpyridinium bromide *(81)* or of phenacylisoquinolinium bromide with *o*-phenylenediamine in boiling glacial acetic acid gives 2-phenylbenzimidazole *(83)* in 62 and 67 % yields, respectively [75].



(81) *(82)* *(83)*

On the other hand, reaction of phenacylquinolinium bromide *(84)* with *o*-phenylenediamine under the same conditions gives an almost quantitative yield of 2-phenyl-3-(*o*-aminophenyl)-1,2-dihydroimidazo[1,2-*a*]quinolinium bromide *(85)*: the electropositivity of the α-position directs the course of the reaction, beginning from the step corresponding to formula *(82)* [72].



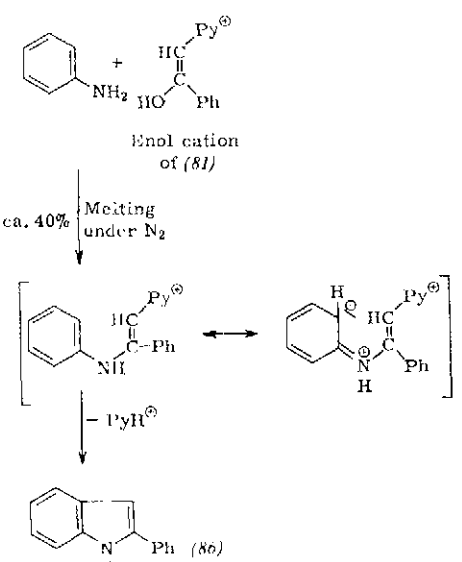
(84) *(85)*

The rearrangement that occurs beginning with the second-last step is well-known in principle [76].

In non-acidic solvents, certain aromatic diamines and hydroquinone form colored molecular compounds with phenacylpyridinium bromide *(81)*, phenacylisoquinolinium bromide, and phenacylquinolinium bromide *(84)*. The molecular compound obtained from benzidine and *(84)* consists of permanganate-colored prisms.

In the reaction of phenacylquinolinium bromide *(84)* with other aromatic amines such as aniline or β-naphthylamine, it is again the α-position that is involved. Under other reaction conditions too, *e.g.* on melting or heating in high-boiling solvents, the dihydroimidazo-[1,2-*a*]quinolinium system is formed [72].

On the other hand, phenacylpyridinium bromide *(81)* and phenacylisoquinolinium bromide yield substituted indoles on reaction with aniline or with *o*- and *p*-toluidine *(86)*. These reactions are best carried out under nitrogen. This fact was simultaneously discovered by *Hirose*, *Takagi*, and *Uno* [77] and by ourselves [75].



(86)

[74] Insertion of the cyano group in the 3-position of the pyridinium nucleus makes the latter generally more similar to "isoquinolinium": *F. Kröhnke*, lecture at the Kolloquium of the Chemisches Institut der Bergakademie Freiberg (Germany) on May 2nd, 1962.

[75] *K. Osterheld*, Diploma thesis, Universität Gießen, 1961.

[76] *F. Kröhnke* and *W. Zecher*, Chem. Ber. *95*, 1128 (1962).

[77] *S. Hirose*, *S. Takagi*, and *T. Uno*, J. pharm. Soc. Japan *81*, 1353 (1961).

In certain cases, this route seems to be more favorable than the so-called Möhlau-Bischler indole synthesis [78] in which ω-bromoketones react with aromatic amines.

V. Errata in Communication No. I, Angew. Chem. *65*, 605 (1953)

Page 607. Left column, footnote 5 is to be completed as follows: *R. C. Fuson*, J. Amer. chem. Soc. *52*, 3269 (1930); *53*, 3494, 4097 (1931); *54*, 1114 (1932).

Page 608. Left column, footnote 26: J. Amer. chem. Soc. *67*, 2089 (1945) instead of J. Amer. chem. Soc. *62*, 2089 (1945).

[78] *R. Möhlau*, Ber. dtsch. chem. Ges. *14*, 173 (1881); *15*, 2480 (1882); 21, 510 (1888); *A. Bischler*, Ber. dtsch. chem. Ges. *25*, 2860 (1892); *A. Bischler* and *P. Fireman*, *ibid. 26*, 1336 (1893); *M. Couper* and *T. St. Stevens*, J. chem. Soc. (London) *1947*, 1041.

Page 608. Right column, footnote 46: *Th. Thomson* u. *Th. Stevens*, J. chem. Soc. (London) *1932*, 69 instead of *1932*, 19.

Page 622. Right column, second-last line of section VII should read: "XIX läßt sich mit Natriumhydrosulfit ..." instead of "XX läßt sich mit Natriumhydrosulfit ..."

Further references to the publications of *C. Marschalk* are German Patent 290984; Frdl. Fortschr. Teerfarb. Fabrikat. *12*, 505 (1914-1916); Bull. Soc. chim. France *1952*, 952, 955.

Sincere thanks are due to the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, the Badische Anilin- und Soda-Fabrik AG., Ludwigshafen, Farbenfabriken Bayer AG., Leverkusen, and the Research Corporation, New York, for the support they have given our research over the years. Frau Lotte Gürich has given me invaluable help in preparation of the manuscript.

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Inorganic Reactions with Arc-heated Gases

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A novel electric-arc device, with a torch consuming 100 to 240 amps DC has been developed. In previous apparatus of this kind, both reactants passed through the arc together, but now only one component (e.g., hydrogen or nitrogen) is heated in this new process. The temperature of this component is raised to a point where it exists in a highly excited state or dissociates into free atoms and then leaves the arc in a stream with supersonic velocity through a hole drilled in the anode, being then mixed with the other reactant. The resultant mixture is then immediately quenched. The design and operation of the torch as well as the mixing and quenching procedures are discussed. The preparation of chlorosilanes, titanium trichloride, titanium nitride, and hydrazine by this method is described.

Introduction

Electrical arcs are used in various fields for the production of high and very high temperatures, *e.g.* for electric arc-welding and -cutting. Several chemical reactions that occur inside electric arcs are also known, such as the old process of "air combustion" for the production of NO (the Birkeland-Eyde or Nitrum process) or the pyrolysis of methane (Hüls process). However, the number of practical processes in which the arc itself serves as reaction site (as in the examples cited above) is limited. Most compounds are completely dissociated at the extremely high temperatures (up to 20 000 °K) prevailing inside the arc; the choice of suitable materials for the torch chamber and the electrodes becomes very difficult in view of corrosion problems, and any control of the reaction by variation of quenching methods and rates is hardly possible.

However, as *Langmuir* proposed long ago, the energy provided by the arc may be stored in a carrier gas (*e.g.*, hydrogen) and utilized afterwards at a point located outside the arc proper. Because of the large heat of dissociation of hydrogen, it is possible to store great quantities of energy in a relatively small volume of gas (see enthalpy curve of hydrogen [1]). In *Langmuir*'s method, the energy contained in the atomic hydrogen is used only in physical operations, such as melting materials with very high melting points. Lately, however, attempts have been made to utilize the heat content of an arc-torch carrier gas to effect chemical reactions.

Thus, in a process developed by *Sennewald*, *Schallus*, and *Pohl* [1], atomic hydrogen is produced in an arc torch and mixed with hydrocarbons. The reaction mixture is then quenched very rapidly, and acetylene is obtained in good yield. This process also avoids formation of useless by-products or by-products which interfere with the separation of the material and which are obtained, for example, in a processes where the hydrocarbons are also made to pass through the arc zone. Lately, inorganic reactions have also been carried out by this

[1] *K. Sennewald*, *E. Schallus*, and *F. Pohl*, Chemie-Ing. Techn. *35*, 1 (1963); *E. Schallus* and *A. Götz*, German Published Patent Application 1012899 (Aug. 1st, 1957).

method [2], but no arrangement has so far been found to permit continuous and prolonged production of large quantities of material.

The aim of the following experiments was to develop pilot-plant scale equipment adapted to continuous operation along the lines just described, and at the same time to find inorganic reactions which could be carried out with advantage by using this process. The following types of reaction were considered:

a) reactions with thermodynamic equilibria which are shifted toward the desired products only at high temperatures (*e.g.*, the preparation of acetylene);

b) reactions in which the products are formed at both high and medium temperatures, but then react very rapidly to yield further products (*e.g.*, the preparation of trichlorosilane or hydrazine);

(In this case, it is advantageous to use an arc-heated gas as energy carrier, since very steep temperature gradients can thus be achieved; *i.e.* the sensitive products are exposed to high temperatures for short periods only.)

c) reactions which require extremely high temperatures in order to achieve commercially practicable conversion rates (*e.g.*, the reduction of titanium tetrachloride with hydrogen);

d) reactions which are customarily run at high temperatures and consequently give rise to difficult corrosion problems (*e.g.*, the reaction of halogens with hydrogen).

(In contrast to conventional high-temperature processes, the walls of the reaction chamber remain cold in the new process.)

In addition to the above subdivision into reaction types, a further distinction must be made: the gas employed as energy carrier may either participate in the reaction (as in the reduction of titanium tetrachloride and tetrachlorosilane) or may serve only as a medium for storing heat (*e.g.* the argon employed in the preparation of hydrazine).

The Apparatus

The Arc Torch

In principle, an electrical arc may be produced with direct current or single- or multiphase alternating current. The use of direct current, however, presents several advantages when employing an enclosed torch chamber.

a) If the stream of gas to be heated is directed axially across a d.c. arc front, a steady, silent, uniform arc is obtained and can therefore be accommodated in an enclosed torch chamber much more easily than alternating or multiphase arcs, which burn irregularly. This also ought to permit higher torch chamber loads.

b) In a d.c. torch, one of the two electrodes can also serve as the torch chamber wall.

c) It is possible to make these electrodes of cooled, practically corrosion-proof metals, so that intricate readjustment mechanisms (required for corrodible electrodes) can be dispensed with.

The direct current torch shown in Fig. 1 was therefore designed along these lines [*]. It consists of a pointed cathode *a*, made of thoriated tungsten, concentrically surrounded by the funnel-shaped copper anode *b*. The rod serving as cathode is held in place by a perforated, water-cooled brass clamp *c*; the gas to be heated (hydrogen, nitrogen, argon, *etc.*) enters at the top of the torch and flows downwards through the perforations, at its high velocity cooling the cathode quite efficiently. The anode is intensively cooled by a water flow of approx. 1 m³/hr. A passage *d* is drilled through the anode to provide an outlet for the hot gases, which pass out from the torch chamber via *d* into a reaction chamber of dimensions suitable for the chemical reaction desired. A ceramic sleeve *e* provides electrical insulation of the cathode from the anode and is installed in such a manner that the arc does not play directly upon it and that the area presented by *e* to radiation from the arc is also small. This insulator is made from a high-melting, low-expansion steatite slip. Polytetrafluoroethylene has been advantageously used for the outer insulation *f*.

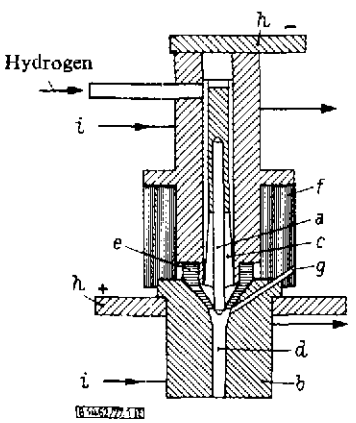

Fig. 1. Direct current arc torch.
a - tungsten cathode; *b* - copper anode; *c* - brass clamp; *d* - outlet nozzle; *e* - ceramic insulator; *f* - outer insulator; *g* - hole for introducing graphite rod (initiator); *h* - power supply connection; *i* - water cooling

The arc is initiated by short-circuiting the electrodes with a thin graphite rod which can be introduced into the torch chamber through a hole *g* in the side of the anode. The arc is stabilized by means of a strong magnetic field coil placed around the torch.

To prevent destruction of the anode by the arc's striking at isolated points (spot arcing), the gases must have a velocity large enough to cause turbulent flow in the boundary layer around the anode. With argon and nitrogen, for example, a velocity of several hundred m/sec suffices but with pure hydrogen, however, velocities of the order of 1000 m/sec become necessary. This is probably due not only to the different flow behavior of hydrogen compared to other gases (Reynolds number), but also to its high thermal conductivity, particularly in the case of atomic hydrogen. Additional design data are given in Table 1.

Table 1. Technical details for the direct-current torch

Current	100 to 250 amps
Arc voltage	100 to 200 volts
Torch output	15 to 30 kilowatts
Rate of gas flow	3 to 5 m³/hr (STP)

[2] *N. C. Cook, D. J. Cobine,* and *J. K. Wolfe,* US-Pat. 2768061 (Oct. 23rd, 1956).

[*] Registered designs DGM 1781880 and 1807595. Dr. *Th. Peters* of the Knapsack Works of the Knapsack-Griesheim AG. was responsible for a large share in its development [3].

[3] *Th. Peters,* Astronautica Acta 7, 150 (1961).

Depending on the anode and the gas velocity, energy losses due to cathode and anode cooling amount to 20–50% at our relatively small torch output of 15 to 30 kilowatts. Larger torches should operate at energy losses no greater than 10–15%. The gas leaves the anode nozzle at supersonic velocities and a temperature of 3000 to over 5000 °C. Thus, almost completely dissociated hydrogen is obtained at normal pressures [4]. Fig. 2 shows a jet of atomic hydrogen leaving the anode nozzle.

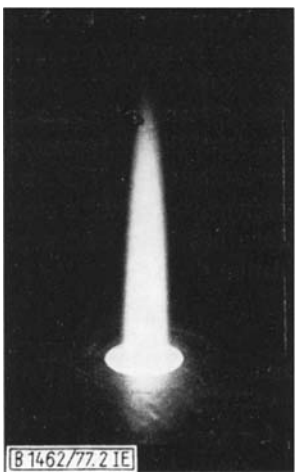

Fig. 2. Arc-heated hydrogen leaving the anode nozzle (nozzle diameter: 8 mm).

Mixing and Quenching Procedure

The yield and frequently also the course of a chemical reaction depend to a large extent on the manner of mixing the arc-heated gas with the other reactant and on the resulting temperature gradient. The method of mixing is therefore of primary practical importance. Despite this, many chemical reactions are still largely controlled by empirical methods, since the pertinent thermochemical, kinetic, flow, and other effects are so interrelated as to be almost inseparable. Quite apart from this general problem, only very few thermochemical and related data are available for the region of high temperatures in question, making reaction control even more difficult.

To achieve the highest possible utilization of the energy contained in the gas leaving the anode, it is necessary to mix in the other reactant directly at the anode nozzle. One possible mixing device consists of a round tube through which the arc gas flows and into which the liquid or gaseous coreactant is pressed through slots directly below the anode outlet. If the rate of flow of the coreactant is sufficiently high, the originally laminar stream of arc gas will be sharply disrupted, and the resulting high turbulence will facilitate rapid mixing of the reactants. It was found that slight modifications in the design of the mixing chamber caused appreciable variations in the composition of the reaction products. Condensation of relatively high-boiling coreactants in the feed tubes of the cooled mixing device is usually undesirable and may be prevented by an appropriate choice of the type and temperature of the coolant. If the coreactant is added in liquid rather than in gaseous form, it can itself serve as coolant. Special adaptations of the above mixer design will be described below in the discussion of the various chemical reactions.

It was already mentioned in the introduction that high-temperature equilibria may be frozen and further reactions may be suppressed by quenching. Two methods of quenching were used. First, liquids were squirted into the hot gas mixture either during the mixing process or immediately afterwards. Thus, the specific heat of the liquid and its even larger heat of vaporization are utilized for rapid cooling of the gas. Very often, however, the lack of chemical inertness of the coolant towards the reaction mixture is detrimental. This effect may be obviated by the use of one of the reactants as the injected liquid coolant (see our experiments for producing hydrazine).

In the second method, the hot mixture is allowed to impinge on a cooled surface located directly in front of the outlet of the mixing device. This surface is prevented from attaining too high a temperature by moving it past the outlet; this is effected, for example, by making it in the form of a rotating cylinder cooled on the inside with water. Such a cooling drum was used successfully in the preparation of chlorosilanes, titanium(III) chloride and titanium nitride as described below.

Chemical Reactions

Reduction of Silicon Tetrachloride

When gaseous silicon tetrachloride is treated with an excess of hydrogen which leaves the anode at about 2900 °C, a mixture is obtained which contains chlorosilanes (SiH_xCl_{4-x}), unreacted silicon tetrachloride, and longer-chain silicon-hydrogen-chlorine compounds [2]. The composition of the mixture of products can be varied by changing the ratios of the rates of flow in the mixing chamber. The composition changes are probably due to variations in the velocity and thoroughness of mixing. When mixing is incomplete, a high proportion of molecules with one or more Si–Si bonds is obtained by pyrolysis of $SiCl_4$ with insufficient hydrogen supply; the average chain length of these products is usually in the range of three to four silicon atoms. With a large excess of hydrogen and good mixing, the percentage of hydrogen-rich chlorosilanes (SiH_2Cl_2, SiH_3Cl, SiH_4), although still relatively low, is nevertheless higher than that obtained when the hydrogen excess is smaller, when relatively large quantities of $SiHCl_3$ are obtained as chief product.

Extremely pure trichlorosilane has achieved importance as the starting material for producing semiconductor silicon. The trichlorosilane (b.p. 33 °C) obtained in the above process can be obtained in an extremely high purity (about 1 ppm of impurities) after only a single fractionation, because the impurities in the technical-grade silicon tetrachloride used are either converted into

[4] *F. Burhorn* and *R. Wienecke*, Z. physik. Chem. *215*, 285 (1960).

volatile hydrides during the reaction or are adsorbed on (or chemically bound to) the longer-chain compounds formed as the by-products of the reaction.

The mixing nozzle used in this reaction is shown in Figure 3.

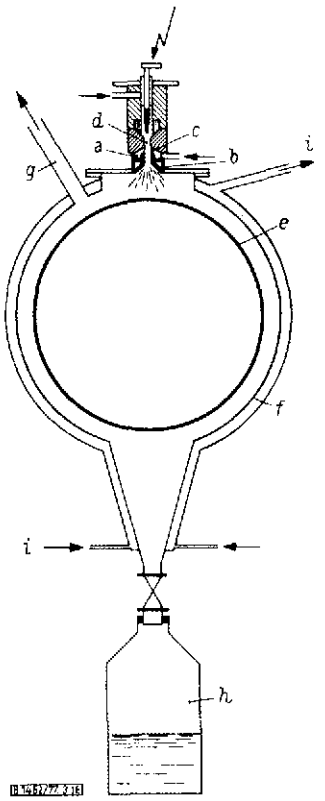

Fig. 3. Gas mixer (including the arc torch).
a - annular space; *b* - mixing device; *c* - circular slit; *d* - anode nozzle; *e* - copper cooling drum; *f* - casing; *g* - tube; *h* - separation vessel; *i* - water cooling

Gaseous silicon tetrachloride is introduced under pressure into the annular channel *a* in the mixing device *b*, and from there it passes through a circular slit *c* into the mixing chamber, where it combines with the jet of hydrogen leaving the anode nozzle *d* with a velocity of about 1000 m/sec. The mixing chamber or nozzle is located above a copper cooling drum *e* (diameter 300 mm) which rotates inside an airtight, water-cooled casing *f*, made of alloy steel. The cooled, gaseous reaction products leave the casing through the tube *g* and flow to a condensation receiver, while higher boiling by-products condense on the surface of the drum and are collected in container *h*.

Up to 70% of an initial charge of 6 to 7 kg/hr of silicon tetrachloride are converted into trichlorosilane ($SiHCl_3$) in a single pass. The greater part of the remaining 30% consists of unreacted silicon tetrachloride, which can be recycled. The space-time yield of the process is extremely high, considering the size of the actual reaction zone within and directly underneath the mixer. The volume of this reactor is only a few hundred cm^3. About a threefold excess of hydrogen is used in this process and can be recycled, following suitable purification. The energy consumption is about 4 kilowatt-hours/kg $SiHCl_3$.

All other processes for reducing silicon tetrachloride with hydrogen which do not incorporate rapid quenching are bound to yield only very little or no trichlorosilane, since at temperatures above 800 °C the product is decomposed further into silicon, silicon tetrachloride, and hydrogen.

Preparation of Lower Titanium Halides

Titanium trichloride is used nowadays as a catalyst for polymerizing olefins and, like the dichloride, in the manufacture of titanium by melt electrolysis. The reduction of titanium tetrachloride to the tri- and dichlorides may be achieved by various methods. These, however, almost always lead to mixtures containing melts [5,6] or solvents [7] and thus necessitate troublesome purification procedures. Although gas-phase reduction with hydrogen becomes feasible above 850 °C, at temperatures below 1200 °C the equilibrium

$$TiCl_{4(gas)} + {}^1/_2\,H_2 \rightleftarrows TiCl_{3(gas)} + HCl \qquad (1)$$

lies so far to the left [8] that the yield of titanium trichloride is too low for a practical industrial process. The equilibrium may be influenced by continually removing the titanium trichloride by means of a "hot-cold" tube, but achievement of a continuous process by this means poses a number of difficult technical problems. The equilibrium shifts towards titanium trichloride only at temperatures above 1300 °C, but then reactions involving the chamber walls begin to occur [8].

If, on the other hand the arc torch and the apparatus depicted in Fig. 3 are used, the high temperatures required are easy to achieve in the gas phase. Simultaneously, reactions with the vessel material are prevented by cooling the walls, higher outputs are achieved by the use of high rates of gas flow, and the process may be made continuous. The only requirements are a scraper to remove the solid titanium halide from the cooling drum and an impingement or a cyclone separator to remove the halide dust suspended in the gas stream. Condensation of unconverted titanium tetrachloride may be prevented by heating the separation device to 50 to 100 °C, depending on the partial pressure of the chloride. Titanium trichloride is obtained in its α-form as the almost exclusive product when the mole ratio of hydrogen to titanium tetrachloride is under 6:1 and the temperature of the hydrogen is kept between 2500 and 3000 °C. If the ratio is increased, then small amounts of titanium dichloride (up to about 10%) appear in the products. The lower halides are obtained in the form of a finely divided, pyrophoric powder, over 99.8% of which consist of titanium and chlorine. Excess hydrogen and unreacted titanium tetrachloride may be recycled after separation of the tetrachloride and removal of the hydrogen chloride. The output ranges up to 6 kg/hr of titanium tetrachloride, the energy consumption is about 5 kilowatt-hours/kg of titanium trichloride, and the conversion per pass is over 60%, based on the tetrachloride charge.

[5] *K. Opp, G. Hamprecht,* and *R. Conrad,* German Pat. 949344 (July 4th, 1953).
[6] *C. E. Rick,* US-Pat. 2856335 (Oct. 4th, 1958).
[7] Esso Research and Engng. Comp., Brit. Pat. 858185 (Jan. 11th, 1961).
[8] *O. Kubaschewski,* Angew. Chem. 72, 225 (1960).

Preparation of Titanium Nitride

Titanium nitride is a highly refractory material and is employed *inter alia* as the powder in plasma flame spraying. The expensive high-temperature method of preparation from titanium powder and nitrogen may be circumvented by treating titanium tetrachloride gas with arc-heated ammonia or nitrogen/hydrogen mixtures, according to the overall equation:

$$TiCl_4 + H + NH_3 \xrightarrow{3000\,^\circ C} TiN + 4\,HCl \qquad (2)$$

It is better still to produce titanium trichloride using arc-heated hydrogen and then to convert it directly into titanium nitride with ammonia in a second step. The reaction product is a very finely divided black powder which contains up to 95% by weight of titanium nitride. The remaining 5% (titanium imides, *etc.*) can be leached out with dilute hydrochloric acid.

The titanium nitride obtained thus gives a crystalline X-ray pattern and has the cubic structure of the δ-phase of the titanium-nitrogen system, with a lattice constant $a = 4.25$–4.26 Å (literature values 4.24 to 4.25 Å [9] at the stoichiometric compositionTiN). Analytical values range from 49.0 to 50.8 atom.% nitrogen. The method therefore yields titanium nitride of almost stoichiometric composition; the black color is attributed to the finely divided state of the product; titanium nitride occasionally separates in the mixing nozzle chamber in the form of large compact crystals that are golden-yellow and shiny. It has the same lattice constant and composition as the finely divided black powder.

Attempts to Prepare Hydrazine

According to recent investigations [10], the formation of hydrazine during a glow discharge in ammonia is due to the reaction of NH radicals with ammonia on the walls of the vessel. Lately, various experiments have been published in which attempts were made to convert ammonia directly into hydrazine by forming such radicals [10–12], thereby avoiding the Raschig process and its variants.

Only small throughputs are possible in the glow discharge process. Since the operating pressure is only a few mm Hg, the large excess of ammonia present must be condensed to a solid together with the hydrazine produced or be continuously removed by means of very large vacuum pumps and compressed before the liquefaction step. The yields are in the range of 0.1–0.2% (based on the ammonia input) or about 5 to 10 g of hydrazine per kilowatt-hour. We therefore attempted to use the arc torch to dissociate or activate ammonia, nitrogen, or argon under normal pressure. The resulting hot gas was mixed with cold anhydrous ammonia and the mixture was then quenched immediately.

Minute amounts of hydrazine are formed even in the purely gas-phase reaction (apparatus of Fig. 3). Thus, a maximum conversion of 0.05% of the ammonia used is obtained, corresponding to 0.2 g of hydrazine per kilowatt-hour. Since hydrazine is very sensitive to heat, inadequate quenching leads to subsequent decomposition of the product into nitrogen and hydrogen.

Quenching which is appreciably more efficient and rapid than that achieved with the aid of a cooling drum may be attained by spraying anhydrous liquid ammonia (−60 °C) under pressure into the high-velocity arc gas jet. The ammonia spray is thus converted into a fine mist of droplets with a very large surface area. Besides providing cooling, the ammonia serves simultaneously as solvent for the hydrazine product. If the liquid phase is then introduced into a packed column from the top and the gaseous phase from the bottom, it is possible (by suitable adjustment of the temperature conditions) to obtain bottoms of liquid ammonia rich in dissolved hydrazine and a gaseous overhead which, after liquefaction, can be recycled to the mixing nozzle. Anhydrous hydrazine can be obtained easily by evaporating off the ammonia from the hydrazine/ammonia mixture. The body of the mixing nozzle is cooled directly by the flow of liquid ammonia. The yield of hydrazine here is increased by a factor of ten (compared to the purely gas-phase reaction) merely by the increased efficiency of quenching, and it might possibly be increased even more by varying other experimental conditions. Nevertheless, owing to the high power consumption, commercial application of this process is at present impractical.

Nitrogen and argon are more effective as arc gases than ammonia, as the latter is completely decomposed in the arc and the resulting large quantities of atomic hydrogen cause decomposition of the hydrazine product. On the other hand, nitrogen and argon form NH radicals upon mixing with ammonia. These react immediately with undecomposed ammonia molecules to give hydrazine. This reaction is particularly favored on the surface of the ammonia droplets.

[9] *M. Hansen* and *K. Anderko:* Constitution of Binary Alloys. 2nd Ed., McGraw-Hill, New York 1958, p. 989.

[10] *H. A. Rathsack*, Z. physik. Chem. *214*, 101 (1960).

[11] Chem. Engng. News *38*, No. 37, 62 (1960).

[12] *J. Robell*, German Published Patent Application 1 084250 (June 30th, 1960).

Received, May 9th, 1962 [B 1462/77 IE]
German version: Chemie-Ing.-Techn. *35*, 7 (1963)

The Biogenesis of Ergot Alkaloids

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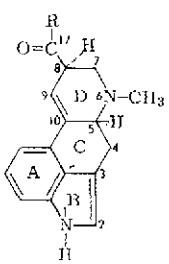
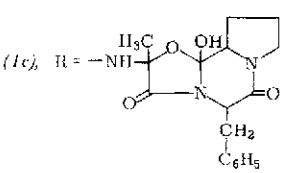
Dedicated to Professor Hans von Euler on the occasion of his 90th birthday

In this article the biogenesis of the ergoline ring in lysergic acid derivatives and the clavines is discussed. Tryptophan and mevalonic acid are the precursors. The N-methyl group is supplied by formate or methionine. Concepts and results dealing with the manner in which the compounds are formed are discussed. Finally, the known biogenetic relationships among the ergot alkaloids are discussed in connection with their biogenesis.

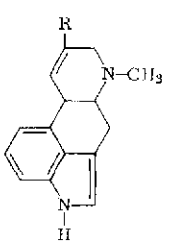
Taken in a wider sense, the ergot alkaloids include the amides of lysergic acid *(1a)* with their unusual cyclic peptides, *e.g.* ergotamine *(1c)*, on the one hand and on the other the clavines, of which agroclavine *(2a)*, elymoclavine *(2b)*, and chanoclavine *(3)* are the most important representatives. Knowledge of their structure is due to the work of *Barger*, *Jacobs*, and *Craig*, and, above



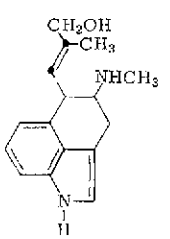
(1a), R = OH
(1b), R = NH_2



(1c), R = —NH—



(2a), R = CH_3
(2b), R = CH_2OH



(3)

all, to that of *Stoll* and *Hofmann* [1]. The clavines have been known only for the past 15 years and have been investigated principally by *Abe* and by *Stoll* and *Hofmann* [2]. Structurally, they are variants of 6,8-dimethylergoline without the peptide portion.

The peptide-containing ergot alkaloids of pharmaceutical interest are obtained even today from ergot cultivated on rye. Although the clavines are formed in fairly large quantities in saprophytic cultures, peptide derivatives are formed in only small quantities. Various attempts have been made to alter this situation by changing either the composition of the media or by other means but with little success so far. Very recently, a variety of *Claviceps paspali* was isolated which produces large quantities of lysergamide and the corresponding *N*-hydroxyethylamide [3].

Early Hypotheses Concerning the Biosynthesis of Ergot Alkaloids

All previous speculations concerning the biogenesis of ergot alkaloids assumed that tryptophan is the starting material, but otherwise they differed considerably. However, none has been proven to be correct.

In their considerations most authors took into account the fact that the 4-position of tryptophan undergoes electrophilic substitutions only with great difficulty. They therefore assumed that a quinoid system is first formed to which the missing carbons are linked. *Van Tamelen* [4] assumed further that an addition product is formed with a dihydronicotinic acid derivative or a similar compound, and that known biochemical reactions take place *via* this addition product.

Harley-Mason [5] also based his hypothesis on a quinoid compound, but then assumed that rings C and D were formed from acetonedicarboxylic acid and formaldehyde.

Plieninger [6] also suggested the addition of an active methylene group to a quinoid system, but gave no further details.

Wendler [7] and *Feldstein* [8], on the other hand, postulated that a ring was closed *via* the carboxylic group of

[1] Reviews on the elucidation of structures: [a] *A. Stoll* in *L. Zechmeister:* Fortschritte der Chemie organischer Naturstoffe. Springer, Vienna 1952, Vol. IX, p. 114; [b] *A. L. Glenn*, Quart. Rev. (Chem. Soc., London) *8*, 192 (1954); Stereochemistry and absolute configuration; [c] *A. Stoll, Th. Petrzilka, J. Rutschmann, A. Hofmann*, and *H. H. Günthard*, Helv. chim. Acta *37*, 2039 (1954); [d] *J. B. Stenlake*, Chem. and Ind. *1953*, 1089; J. chem. Soc. (London) *1955*, 1626; [e] *H. G. Leemann* and *S. Fabbri*, Helv. chim. Acta *42*, 2696 (1959); Syntheses: [f] *E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones*, and *R. B. Woodward*, J. Amer. chem. Soc. *78*, 3087 (1956); [g] *A. Hofmann, A. J. Frey*, and *H. Ott*, Experientia *17*, 206 (1961).

[2] For bibliographies, see *e.g. M. Abe* in: 2. Arbeitstagung über Biochemie und Physiologie der Alkaloide, Halle (Saale) 1960. In the press.

[3] *F. Arcamone, E. B. Chain, A. Ferretti, A. Minghetti, P. Pennella, A. Tonolo*, and *L. Vero*, Proc. Roy. Soc. (London), Ser. B, *155*, 26 (1961).

[4] *E. E. van Tamelen*, Experientia *9*, 457 (1953).

[5] *J. Harley-Mason*, Chem. and Ind. *1954*, 251.

[6] *H. Plieninger*, Experientia *14*, 57 (1958).

[7] *N. L. Wendler*, Experientia *10*, 338 (1954).

[8] *A. Feldstein*, Experientia *12*, 475 (1956).

tryptophan. *Wendler* thought that the subsequent condensation involved citric acid, whereas *Feldstein* thought it was *via* α-ketoglutaric acid.

Finally, *Robinson* [9] suggested that tryptophan and succinic acid first undergo Claisen condensation, the missing carbon atom being supplied by formaldehyde.

Studies with Radioactive Tracers

Our starting point was the work by *Gröger* and *U. Mothes* [10] which showed that when tryptophan was injected into the phloem of rye plants, the yield of ergot alkaloids was greatly increased. In collaboration with *K. Mothes* and his group, we began our studies using compounds labelled with ^{14}C and ^{3}H.

Our first experiments consisted of injecting DL-[β-^{14}C]-tryptophan into the internodes of rye plants which had been raised in a greenhouse and which had been infected with *Claviceps purpurea*. We succeeded in isolating radioactive alkaloids and in hydrolysing them to radioactive lysergic and isolysergic acids [11].

At about the same time, *Suhadolnik* and coworkers [12] carried out similar experiments in the USA and concluded that tryptophan is not a precursor in the biosynthesis of ergot alkaloids. It has not been explained why they did not obtain positive results.

We then repeated our work with ergot grown on rye in the field infected with *C. purpurea*, strain XXVII, and obtained a rate of incorporation [*] of 0.16 % and a specific rate of incorporation [**] of 3.21 %. Undoubtedly these figures would have been higher if it had been possible to base them on the amount of tryptophan that had actually reached the sclera.

Using fungi cultures in the laboratory, we obtained the results shown in Table 1. The rate of incorporation of DL-[β-^{14}C]-tryptophan was raised to 47.5 % by the use of replacement cultures [***] [14].

These studies showed that the ergoline ring was made up not only from the L-form, but also, to some extent, from the D-form (racemase?) [15]. Apparently tryptophan undergoes decarboxylation in the course of the synthesis of the alkaloids, since tryptophan labelled with ^{14}C in the carboxyl group gave rise exclusively to non-radioactive alkaloids [13, 14]. Since then, other research teams have confirmed that tryptophan is the precursor of ergot alkaloids [16–20].

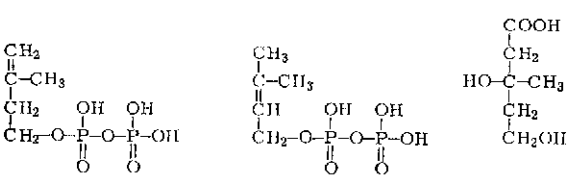
Table 1. Incorporation of radioactively labelled tryptophan and indole into ergot alkaloids by saprophytic cultures of *Claviceps purpurea*, strain SD 58. The strain preferentially forms elymoclavine in addition to agroclavine and penniclavine. The total alkaloids were isolated.

	Compound administered	Rate of incorporation
Surface cultures	DL-[β-^{14}C]-tryptophan	10.7–39.4 % on adding increasing quantities of pyridoxal phosphate [13]
	D-[Ar-^{3}H]-tryptophan	14 % [15]
	DL-[carboxyl-^{14}C]-tryptophan	no incorporation [13, 14]
Replacement cultures	DL-[β-^{14}C]-tryptophan	47.5 % [14]
	^{3}H-indole	5.5–24 % in elymoclavine [*] [15]

[*] Specific rate of incorporation.

In our experiments with saprophytic cultures, we also found that [1-^{14}C]-acetate is utilized in the biosynthesis of the alkaloids with rates of incorporation of up to 0.3 % [13]. This result was in accordance with our hypothesis [11] that the five missing carbon atoms are derived from an isoprenoid compound. This hypothesis received further support from the elucidation of the structure of chanoclavine *(3)*, accomplished a short time earlier [21]. Its open D-ring structure is in good agreement with our assumption.

Isopentenyl pyrophosphate *(4)* and its isomer dimethylallyl pyrophosphate *(5)* have been recognized by *Bloch* and by *Lynen* as "active isoprene"; these originate from mevalonic acid *(6)*, the acetate replacing factor discovered by *Folkers* [22]. We were able to show that [2-^{14}C]-mevalonic acid is utilized for alkaloid synthesis with a specific rate of incorporation of 16 % [23]. This was the first demonstration that mevalonic acid is used



(4) *(5)* *(6)*

[9] *R. Robinson*, The Structural Relations of Natural Products. The Clarendon Press, Oxford 1955, p. 7.

[10] *D. Gröger* and *U. Mothes*, Pharmazie *11*, 323 (1956).

[11] *K. Mothes, F. Weygand, D. Gröger*, and *H. Grisebach*, Z. Naturforsch. *13b*, 41 (1958).

[12] *R. J. Suhadolnik, L. M. Henderson, J. B. Hanson*, and *Y. H. Loo*, J. Amer. chem. Soc. *80*, 3153 (1958).

[*] The rate of incorporation is defined as $\frac{\text{total activity of product} \times 100}{\text{total activity of the precursor}}$ [%]

[**] The specific rate of incorporation is defined as $\frac{\text{specific molar activity of product} \times 100}{\text{specific molar activity of the precursor}}$ [%]

[***] A replacement culture is washed mature mycelium suspended in a medium which suppresses further substantial vegetative growth.

[13] *D. Gröger, H. J. Wendt, K. Mothes*, and *F. Weygand*, Z. Naturforsch. *14b*, 355 (1959).

[14] *D. Gröger, K. Mothes, H. Simon, H.-G. Floß*, and *F. Weygand*, Z. Naturforsch. *15b*, 141 (1960).

[15] *D. Gröger, K. Mothes, H. Simon, H.-G. Floß*, and *F. Weygand*, Z. Naturforsch. *16b*, 432 (1961).

[16] *W. A. Taber* and *L. C. Vining*, Chem. and Ind. *1959*, 1218.

[17] *R. M. Baxter, S. I. Kandel*, and *A. Okany*, Chem. and Ind. *1960*, 266.

[18] [a] *H. Plieninger, R. Fischer, W. Lwowski, A. Brack, H. Kobel*, and *A. Hofmann*, Angew. Chem. *71*, 383 (1959).
[b] *H. Plieninger, R. Fischer, G. Keilich*, and *H. D. Orth*, Liebigs Ann. Chem. *642*, 214 (1961).

[19] *L. R. Brady* and *V. E. Tyler jr.*, Planta med. *7*, 225 (1959).

[20] *F. Arcamone, E. B. Chain, A. Ferretti, A. Minghetti, P. Pennella*, and *A. Tonolo*, Biochim. biophysica Acta *57*, 174 (1962).

[21] *A. Hofmann, R. Brunner, H. Kobel*, and *A. Brack*, Helv. chim. Acta *40*, 1358 (1957).

[22] Review: *A. F. Wagner* and *K. Folkers*, Endeavour *20*, 177 (1961).

[23] *F. Weygand*, Angew. Chem. *71*, 383 (1959).

not only for the synthesis of typical isoprenoid compounds, but also for the biosynthesis of alkaloids.

Further experiments have shown that both [2-^{3}H]-mevalonic acid and [4-^{3}H]-mevalonic acid are incorporated into clavines [14]. It therefore seems probable that mevalonic acid is utilized without prior decomposition into smaller compounds.

Other workers [24–27] have confirmed our results with mevalonic acid. *Birch* also found that [2-^{14}C]-mevalonic acid is incorporated into agroclavine and elymoclavine. By Kuhn-Roth oxidation and degradation of the resulting acetic acid the activities of the CH_3 and the $-CH_2OH$ groups were determined; the latter was first reduced to a methyl group. *Birch* obtained the surprising result that C-17 of elymoclavine contained 90% of the total radioactivity, whereas C-17 of agroclavine contained only 33%. In a later paper [25], however, he showed that in both compounds C-17 contained the bulk of the activity. *Baxter* and coworkers [27] obtained similar results by degradative studies on the lysergic acid derivative ergosine, obtained biosynthetically from [2-^{14}C]-mevalonic acid.

The experiments of *Baxter et al.* [27a] and of *Plieninger* [18b] furthermore lead to the conclusion that mevalonic acid is incorporated into ergot alkaloids *via* isopentenyl or dimethylallyl pyrophosphate, as is the case with terpenes. In *Baxter*'s experiments, the presence of non-radioactive isopentenyl and dimethylallyl pyrophosphate lowered the rate of incorporation of [2-^{14}C]-mevalonic acid. In addition, experiments with [1-^{14}C]-mevalonic acid demonstrated the non-incorporation of the carboxyl group. *Plieninger* found that deuterated isopentenyl pyrophosphate is incorporated into clavines.

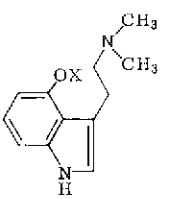
The origin of the carbon atom at the *N*-methyl group could be shown with a great degree of certainty by *Baxter* [28]. The methyl group of methionine labelled with ^{14}C as well as [^{14}C]-formate were incorporated. Degradation of festuclavine obtained from these labelled precursors showed that the *N*-methyl group contained all of the radioactivity [29]. The higher rate of incorporation of [Me-^{14}C]-methionine and the incorporation of [Me-^{14}C,^{3}H]-methionine without alteration of the ratio ^{14}C:^{3}H indicated that the *N*-methyl group can result from methionine by transmethylation. Probably, the biosynthesis also takes this course.

The experiments described so far have elucidated the origin of the entire carbon skeleton of the ergot alkaloids. It was now of interest to determine the manner in which the known precursors are joined together and also to determine the biogenetic interrelationships of the various ergot alkaloids, particularly between the clavines and the lysergic acid derivatives.

Formation of Rings C and D

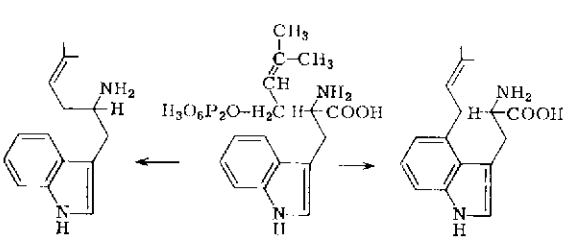
The formation of rings C and D poses a question that is particularly difficult to answer, as it seemed reasonable to believe that electrophilic substitution of the indole ring in position 4 is difficult. Whereas many 5-substituted indoles do occur in nature the number of natural 4-substituted derivatives is extremely small. Both *Plieninger* [18b] and *Baxter* [17] were able to disprove the earlier supposition that the 4-position is activated by a hydroxyl group in position 5.

The discovery of the fungal metabolites psilocine *(7)* and psilocybine *(8)* [30] was of particular interest in this connection, as it was shown shortly afterwards that these indole derivatives, which are hydroxylated in the 4-position, are derived from tryptophan [31].



(7), X = H
(8), X = PO_3H_2

These findings therefore demonstrated that tryptophan can be hydroxylated in the 4-position in nature, and gave rise to the supposition that such a reaction may also play a part in the biosynthesis of the ergot alkaloids [31]. Another possibility is the occurence of a direct condensation of tryptophan with "active isoprene", presumably dimethylallyl pyrophosphate. Such a reaction may occur by one of two ways, either by attack at the 4-position of the indole ring system, leading to the formation of 4-dimethylallyltryptophan *(10)* [25] or by attack at the α-carbon atom of the tryptophan side-chain with simultaneous decarboxylation giving compound *(9)*. In the first case, the condensing enzyme must in some way cause the reaction to occur at position 4 instead of at the electronically favored positions 5 or 7. In the second, preference for position 4 results from arrangement of the carbon atoms in *(9)*, since for stereochemical reasons, position 5 cannot be attacked during cyclization.



(9) *(10)*

[24] *A. J. Birch, B. J. McLoughlin*, and *H. Smith*, Tetrahedron Letters *1960*, No. 7, p. 1.

[25] *S. Bhattacharji, A. J. Birch, A. Brack, A. Hofmann, H. Kobel, D. C. C. Smith, H. Smith*, and *J. Winter*, J. chem. Soc. (London) *1962*, 421.

[26] [a] *E. H. Taylor* and *E. Ramstad*, Nature (London) *188*, 494 (1960).
[b] *E. H. Taylor* and *E. Ramstad*, J. pharmac. Sci. *50*, 681 (1961).

[27] [a] *R. M. Baxter, S. I. Kandel*, and *A. Okany*, Tetrahedron Letters *1961*, 596.
[b] *R. M. Baxter, S. I. Kandel*, and *A. Okany*, J. Amer. chem. Soc. *84*, 2997 (1962).

[28] *R. M. Baxter, S. I. Kandel*, and *A. Okany*, Chem. and Ind. *1961*, 1453.

[29] *S. I. Kandel, R. M. Baxter, A. Okany*, and *K. L. Tam*, Lecture delivered at the International Symposium on Organic Chemistry of Natural Products, Brussels 1962.

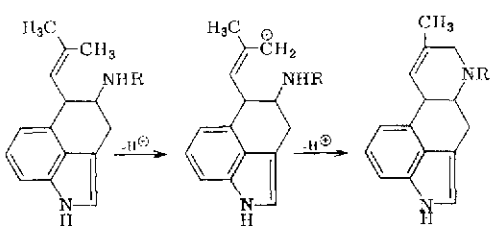
[30] *A. Hofmann, R. Heim, A. Brack, H. Kobel, A. Frey, H. Ott, Th. Petrzilka*, and *F. Troxler*, Helv. chim. Acta *42*, 1557 (1959).

[31] *A. Brack, A. Hofmann, F. Kalberer, H. Kobel*, and *J. Rutschmann*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *294*, 230 (1961).

Although some experimental studies have been carried out, the question of the formation of the ergoline ring system is still largely unexplored. Experiments by *Baxter* [28,29] as well as ours [32] have shown that probably neither tryptamine nor *N(α)*-methyltryptophan nor *N(ω)*-methyltryptamine take part in the biosynthesis of the alkaloids. Hence, the condensation of tryptophan with an active isoprene is preceded by neither decarboxylation nor by methylation. Experiments using 4-hydroxytryptophan have, as yet, not been published. Recently, *Plieninger* [33] synthesized 4-dimethylallyl-[^{14}C]-tryptophan *(10)* and observed that this compound is utilized in the formation of elymoclavine with a specific rate of incorporation of 4.2 %. We in turn synthesized compound *(9)* with a tritium label in the indole nucleus. This compound, too, led to labelled elymoclavine with a rate of incorporation of 20–33 % [34]. Because the results with these two precursors are not comparable, ^{14}C-labelled compound *(10)* and ^{3}H-labelled compound *(9)* were added together to cultures of ergot fungus. The experiments were carried out under different experimental conditions in Heidelberg, Munich, and, by *D. Gröger*, in Halle (Germany). All of them showed that *(10)* is always utilized better than *(9)*. The ratio at which these two precursors were utilized varied between 1.6:1 and 87:1 [expressed in terms of *(10)*:*(9)*]. The rates of incorporation for *(10)* varied between 3.5 and 20 %, and those for *(9)* between 0.04 and 5 %. So far we have been unable to reproduce the high rates of incorporation previously found for compound *(9)*. The reasons for this are still unknown [*]. On the other hand, the rates of incorporation of dimethylallyltryptophan into alkaloids are not higher than those commonly encountered under comparable conditions with tryptophan. If compound *(10)* is synthesized subsequent to tryptophan in the biosynthetic pathway, one would expect it to be utilized to a greater extent than the latter. Problems of permeability and the like may of course play a role here.

One may imagine that rings C and D are formed from a condensation of tryptophan and active isoprene, *i.e.* compound *(9)* oder *(10)* or a similar compound, and that this condensation product undergoes dehydrogenation at the methylene group in the allyl position, and that the allyl cation adds on electrophilically in position 4 or in the side chain to give compound *(11)*. Another allyl cation can be formed at the *cis*-methyl group *(12)* and ring closure with the amino group would then lead to ring D.

Other transformations of the clavine alkaloids can also be explained by such allyl dehydrogenations and subsequent steps, *e.g.* allyl rearrangement and hydroxylation.



(11) *(12)* *(2c)*

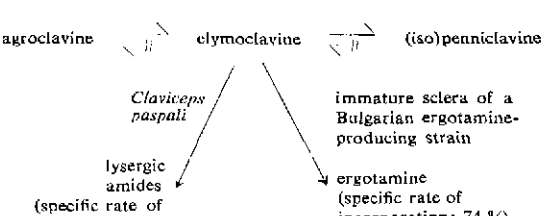
Biogenetic Interrelationships

It is much simpler to explain biogenetic interrelationships between ergot alkaloids by means of isotope studies. There are originally two mainpoints of view: According to *Abe* [2], all ergot alkaloids are supposed to originate from a common precursor, the C-17 aldehyde, which is oxidized to lysergic acid on the one hand and which undergoes reduction to elymoclavine, agroclavine, and chanoclavine on the other. The other opinion, formulated for example by *Rochelmeyer* [35], considers the clavines to be precursors of lysergic acid. *Abe*'s opinion became untenable when it was found that [2-^{3}H]-mevalonic acid is incorporated into the clavines nearly as readily as [2-^{14}C]-mevalonic acid [14]. Since carbon 2 of mevalonic acid becomes C-17 of the clavines, then if *Abe*'s hypothesis were correct, the loss of tritium should have been substantial. That this is not the case was recently confirmed by *Baxter* [29]. Some clarification then came from work by *Agurell* and *Ramstad* [36], who were able to demonstrate the following sequence of reactions by means of studies with a strain of *Claviceps*:

agroclavine → elymoclavine → (iso)penniclavine.

Each of these steps proved irreversible. This eliminated the possibility of clavine-formation by way of reduction.

Recently, it has been demonstrated [37] that transformation of elymoclavine into lysergic acid derivatives can be accomplished biologically. This transformation was demonstrated by application of [^{3}H]-elymoclavine to the sclera of a strain of rye ergot, using the method of *Winkler* and *Mothes* [38], which gave rates of incorporation of up to 74 %. It was also achieved using submerged cultures of a strain of *Claviceps paspali*, which forms simple lysergic amides. The specific rates of incorporation of elymoclavine were up to 30 %. These experiments make it probable that lysergic acid derivatives can be formed oxidatively from clavines (Scheme 1).



Scheme 1. Formation of lysergic acid derivatives from clavines

[32] *D. Gröger, K. Mothes, H.-G. Floß*, and *F. Weygand*, unpublished data.

[33] *H. Plieninger, R. Fischer*, and *V. Liede*, Angew. Chem. internat. Edit. *1*, 399 (1962).

[34] *F. Weygand, H.-G. Floß*, and *U. Mothes*, Tetrahedron Letters *1962*, 873.

[*] It should be mentioned in this connection that the fungus strain we used practically stopped producing alkaloids soon after our first experiments with compound *(9)*. Because of this we are unable to reproduce accurately the conditions of our earlier experiments.

[35] *H. Rochelmeyer*, Pharmaz. Ztg. *103*, 1269 (1958).

[36] *S. Agurell* and *E. Ramstad*, Tetrahedron Letters *1961*, 501.

[37] *K. Mothes, K. Winkler, D. Gröger, H.-G. Floß, U. Mothes*, and *F. Weygand*, Tetrahedron Letters *1962*, 933.

[38] *K. Winkler* and *K. Mothes*, Planta med. *10*, 208 (1962).

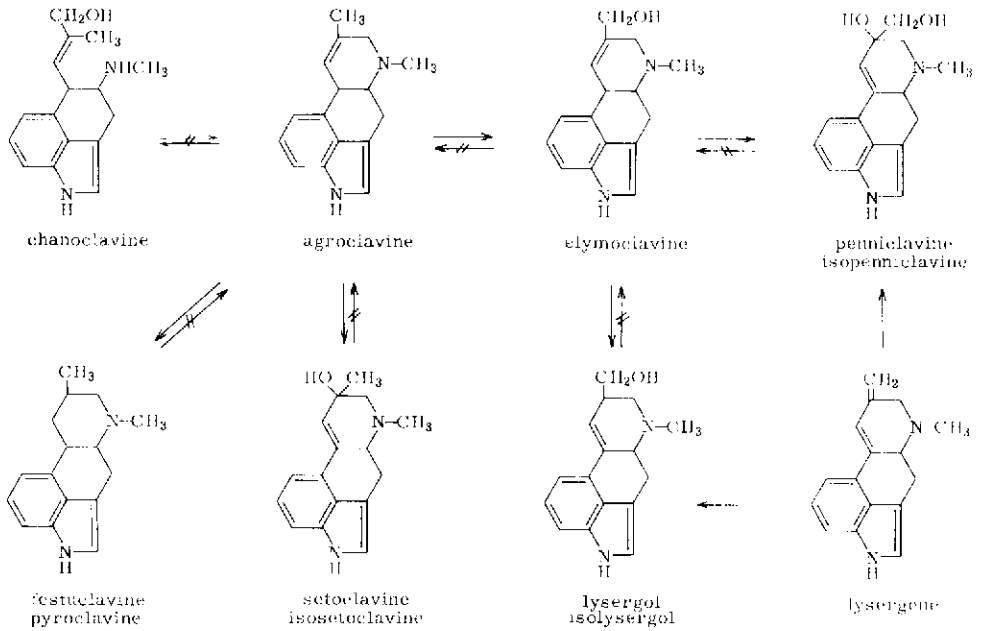
In the meantime, *Agurell* and *Ramstad* [39] have succeeded in elucidating the biogenetic interrelationships between numerous clavine alkaloids; *Baxter et al.* [29] have come to similar conclusions (Scheme 2).

Accordingly, most clavines are derived from agroclavine and elymoclavine. The epimers at C-8, which are formed in the course of these transformations, *e.g.* penniclavine and isopenniclavine, cannot be interconverted. They therefore appear to originate independently. It is also interesting to note that the transformation of agroclavine into setoclavine, and of elymoclavine into penniclavine and isopenniclavine can be accomplished not only with the aid of various strains of *Claviceps*, but also with the Mexican fungus *Psilocybe semperviva* [40].

Finally, some remarks should be made concerning the peculiar position of chanoclavine among the ergot alkaloids. It has been considered both as a precursor and as a by-product of the alkaloids of the clavine type, but may also represent the product resulting from the opening of the D-ring. *Baxter* [29] has reported that chanoclavine did not arise from agroclavine in the course of his experiments, nor did it give rise to the latter. *Agurell* and *Ramstad* [39] arrived at similar conclusions. Consequently, in the cases studied, chanoclavine does not appear to be a precursor in the biosynthesis of clavines which possess a closed D-ring.

Mothes and *Winkler* [41] recently obtained quite remarkable results. They found that after application of [^{3}H]- and [^{14}C]-elymoclavine to ripening sclera not only was the ergotamine labelled, but also the chanoclavine, which had a specific rate of incorporation of 40 %. This demonstrates that chanoclavine can arise by ring opening.

Attention is called to the fact that, on the basis of our work, this pathway is probably not the only one leading to chanoclavine. We found that after addition of tritium-labelled tryptophan to a surface culture of *Claviceps* and isolation of the resulting alkaloids, *viz.* chanoclavine, agroclavine, elymoclavine, and penniclavine, the chanoclavine had a much higher specific activity than any of the other three alkaloids [42]. Hence chanoclavine cannot possibly have originated from the other three compounds. It is noteworthy in this connection that, according to *Arigoni* [43], the hydroxymethyl group of chanoclavine is *trans* with respect to ring C. We therefore assume that chanoclavine can also be formed by a side reaction, *i.e.* that oxidation which normally serves to convert agroclavine into elymoclavine occurs before ring D is closed.



Scheme 2. Biogenetic interrelationships between some clavine alkaloids

Received, December 11th, 1962 [A 282/85 IE]

[39] *S. Agurell* and *E. Ramstad*, Arch. Biochem. Biophysics *98*, 457 (1962).

[40] *A. Brack*, *R. Brunner*, and *H. Kobel*, Helv. chim. Acta *45*, 276 (1962).

[41] *K. Mothes* and *K. Winkler*, Tetrahedron Letters *1962*, 1207.

[42] *F. Weygand*, *H.-G. Floß*, and *U. Mothes*, unpublished results.

[43] *D. Arigoni*, personal communication.

Macromolecules with Non-uniform Solubilities – Heterogels and Heteropolymers [*]

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It is possible to produce chain-like macromolecules A–B, with A and B parts which have different solubilities in a given solvent. In solvents, depending on the concentration, the insoluble parts of these non-uniformly soluble macromolecules form micelles, aggregates, cylinders, or layers, while the soluble parts and the solvent fill up the gaps. The structure of these heterogels is destroyed by stirring or heating, but it can be fixed by polymerizing the solvent.

1. Introduction

If a chain-like copolymer derived from monomers a and b contains only short stretches in which several units of either a or b are linked together in sequence, then the molecule behaves practically like a homogeneous chain. If, however, the copolymer contains long parts that are built up alternately, from only a or b, its properties can be described, more or less accurately, by a combination of the properties of the homopolymers a and b.

It is interesting to see how the properties of such a copolymer vary as a function of the length and statistical distribution of the homogeneous sequences $(a)_i$ and $(b)_j$. It can be assumed that a molecule with two long sequences a-a-a....a-b....b-b-b, – in brief, A-B, – possesses solubility characteristics in each particular range which are similar to those of a chain made up from pure a or b, respectively. Part A of the copolymer will therefore behave towards a solvent S just like a homopolymer made up of a, and part B just like a homopolymer made up of b. The molecule A-B has therefore heterogeneous solubility properties and is described here as being "non-uniformly soluble".

In the following, only molecules with two sequences (A-B) will be dealt with. Binary copolymers with more complex structures, *e.g.* with three or four sequences (A-B-A or A-B-A-B), have also been investigated, but they are not essentially different from copolymers of the type A-B.

The most likely shape for an open-chain molecule in solution is that of a tangled string that is looser in a good solvent and tauter in a bad one. Theory and the interpretation of experimental results give the following relationship for the mean square of the distance between the ends of a long flexible chain-like molecule of mass M:

$$\overline{r^2}_M = b^2 \left(\frac{M}{m}\right)^{1+\varepsilon}$$

The value of b depends on the length of the units of the macromolecule, m is the mass of these units, ε is determined by the second virial coefficient of the solution. The value of ε is therefore influenced by the thermodynamic interaction between the molecules of the solute and of the solvent as well as by temperature. Generally speaking, for very good solvents, *i.e.* for loosely tangled macromolecules, ε has values of the order of $1/3$. There is a temperature for each solvent at which ε equals zero.

[*] Lecture given at the XIVth International Plastics Congress, which took place together with the 12th International Engineering Exhibition, from Sept. 27th to 29th, 1962 in Turin (Italy).

2. Micellar Solutions and Heterogels

Classical soaps are examples of molecules with non-uniform solubility. The polar end-group is readily soluble in water, for instance, while the hydrocarbon residue is not.

If part A of a copolymer A-B is soluble in a solvent S, and part B is insoluble, and if A forms only a small proportion of the macromolecule, the copolymer A-B will be insoluble in S. Solubility can only be attained by increasing the ratio m_A/m_B. In other words, solubility depends on the relationship between the total mass M_{A-B} of the molecule A-B and the masses of its parts m_A and m_B. If A-B is completely soluble in S and if the two parts of the molecule behave effectively as if they existed independently, the soluble part A should form a loosely tangled ball and B a more or less compact nucleus (Fig. 1).

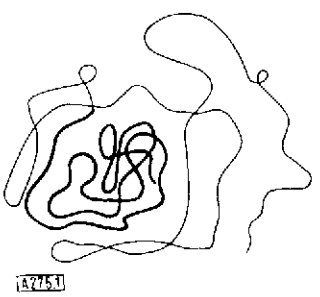

Fig. 1. Monomolecular micelle of a chain molecule with non-uniform solubility. The less soluble part of the molecule (thick line) forms the compact nucleus of a loose tangle of the more soluble part of the molecule (thin line).

Monomolecular micelles of this kind can only be observed at high dilutions, as the insoluble parts of several molecules tend to associate with increasing concentration. Above a certain concentration which depends on the chemical nature of A, B, and S and on the ratio by weight $M_{A-B}:(m_A/m_B)$, aggregates are formed in

solution. These consist of nuclei which are formed from the B parts of several molecules and which are surrounded by loose tails of A parts. The suspension thus consists of multimolecular micelles.

If the concentration is still higher, the aggregates organize themselves in a regular structure. The insoluble parts B form parallel layers or parallel cylinders of homogeneous material, dispersed in an interstitial medium formed by the solution of A in S (Fig. 2). In general one observes cylinders (Fig. 2a) at lower and layers (Fig. 2b) at higher concentrations. Both structures are actually mesomorphous gels.

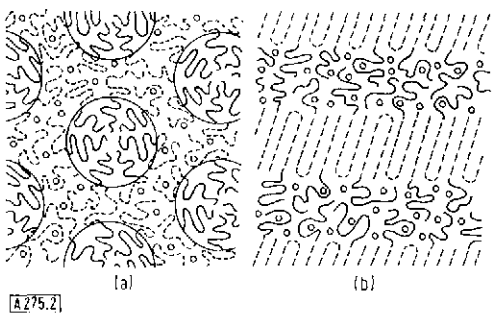

Fig. 2. Structure of a copolymer of type A-B made from polystyrene and polyoxyethylene (a) in nitromethane (cylindrical structure) and (b) in butyl phthalate (layer structure). Nitromethane dissolves preferentially the polyoxyethylene part, butyl phthalate the polystyrene part.
——— polystyrene part
- - - - - - polyoxyethylene part
o solvent.

Thus, with increasing concentration, the following shapes arise in succession: monomolecular micelles, multimolecular micelles or aggregates, organized cylindrical structures, and finally organized layer structures. At some concentrations, several shapes can exist side by side. Moreover, their succession is influenced by temperature.

An example of a copolymer A-B with non-uniform solubility is the linear macromolecule consisting of a polystyrene (A) and a polyoxyethylene chain (B). The degree of polymerization of A and B can vary between some tens and several hundreds. The reaction takes place according to a process described by *Richards* and *Szwarc* [1].

Polystyrene is prepared by anionic polymerization at −80 °C in homogeneous phase, [solvent: tetrahydrofuran; initiator: phenylisopropylpotassium *(1)*]. A chain terminating in a carbanion is obtained *(2)*. On addition of ethylene oxide, *(3)* is formed first. The solution is then heated in small portions under pressure to 80 °C for 48 hours.

$$H_5C_6-C(CH_3)_2-K \qquad (1)$$

$$\cdots CH_2-CH(C_6H_5)-K \rightleftarrows \cdots CH_2-\overset{\ominus}{C}H(C_6H_5) + K^{\oplus} \qquad (2)$$

$$\cdots CH_2-CH(C_6H_5)\cdots CH_2-CH_2\cdots OK \qquad (3)$$

The copolymer obtained is washed in order to remove any homopolymer formed by a side reaction.

This process can also be applied to the preparation of copolymers of the type B-A-B. An indirect method [2] has to be used for the preparation of A-B-A and $(A\text{-}B)_n$ types.

The solubilities of the polyoxyethylene and the polystyrene chains differ in most solvents. If, for instance, 80 parts of a copolymer consisting of 41% polystyrene (A) and 59% polyoxyethylene (B) (aggregate molecular weight: 13600) are dissolved in 100 parts of butyl phthalate, which is a good solvent for polystyrene, a gel with a layer strueture is formed at room temperature. The polyoxyethylene parts, which are only slightly soluble in butyl phthalate, form crystalline layers, 105 Å thick. The polystyrene parts and the solvent are interspersed in layers 110 Å thick.

If 60 parts of this copolymer are treated with 100 parts of nitromethane as solvent at room temperature, a mesomorphous gel of parallel cylinders is formed. These cylinders consist of the polystyrene parts of the copolymer, which are insoluble in nitromethane, while the space between them is occupied by the solution of the polyoxyethylene parts in nitromethane (Fig. 2a). The distance between the axes of any two cylinders is 163 Å, the diameter of the cylinders is 90 Å.

In both cases, therefore, heterogels are obtained in the form of highly viscous liquids. As can be seen in the polarization microscope (Fig. 3), they are made up of

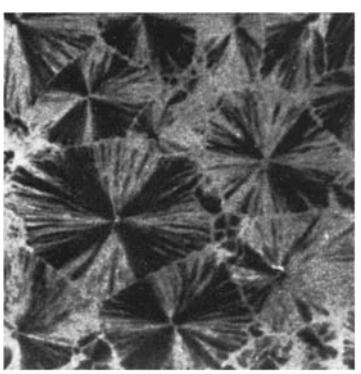

Fig. 3. Anisotropic micro-ranges of a liquid heterogel under the polarization microscope.

small, markedly anisotropic ranges. The X-ray diagram of this type of heterogel shows a black coloration at the centre, which can be ascribed to the presence of small ranges each with a uniform layer or cylindrical structure [3–5].

3. Heteropolymers

a) Non-ionic Heteropolymers

Mesomorphic heterogels are unstable. Agitation or heating destroys their structure. If the solvent is replaced by a polymerizable monomer and the latter polymerized, the gel's structure is fixed. A solid polymer of high stability is formed, with the heterogeneous character of

[1] *D. H. Richards* and *M. Szwarc*, Trans. Faraday Soc. *55*, 1644 (1959).

[2] *G. Finaz*, *P. Rempp*, and *J. Parrod*, Bull. Soc. Chim. France *1962*, 262.

[3] *A. Skoulios*, *G. Finaz*, and *J. Parrod*, C. R. hebd. Séances Acad. Sci. *251*, 739 (1960).

[4] *A. Skoulios* and *G. Finaz*, C. R. hebd. Séances Acad. Sci. *252*, 3467 (1961).

[5] *A. Skoulias* and *G. Finaz*, J. Chim. physique *1962*, 473.

a system A-B/S. After polymerization of S, the polymer contains as inclusions the micelles, aggregates, cylinders, or layers that had existed in the gel before polymerization. A heteropolymer with organized structure [6] is thus obtained.

Some examples are shown in Table 1. Experience shows [7] that polymerization does not cause disintegration of the gel structure, but only a minor alteration of the structural parameters.

Table 1. Heteropolymers formed from a copolymer of 41 % polystyrene and 59 % polyoxyethylene. With the exception of acrylic acid, the monomeric solvent dissolves preferentially the polystyrene part.

Monomeric solvent	Gel structure	Polymerization initiated by
Methyl methacrylate	layer	ultraviolet light
Isoprene	layer	BF_3
Vinyl acetate	layer	ultraviolet light
Acrylonitrile	layer	ultraviolet light
Propylene oxide	layer	ultraviolet light plus azo-bis-isobutyronitrile
Acrylic acid	cylindrical	ultraviolet light

If, for example, 32 parts of the polystyrene/polyoxyethylene copolymer are mixed with 100 parts of acrylic acid, which preferentially dissolves the polyoxyethylene part, a gel with cylindrical structures is formed. The cylinders consist of the polystyrene parts, the intervening space is filled by the polyoxyethylene/acrylic acid mixture. If a thin layer of this gel is irradiated between two mica plates with ultraviolet light, after addition of some azo-bis-isobutyronitrile as photosensitizer, solidification of the layer takes place within about 48 hours, without any change in its mesomorphous structure (diameter of cylinders 105 Å, inter-axial distance between neighboring cylinders 152 Å).

The cylindrical structure has thus been fixed. It is now stable to mechanical wear and also resists temperature changes. If the sample is heated, the structure is retained up to about 250 °C, where it begins to melt and decompose. It appears that the structure is reformed on cooling, in part at least. Generally speaking, large structures fixed by the polymerization are less stable than fixed cylindrical structures.

b) Ionized Heteropolymers

A molecule A-B with non-uniform solubility can also consist, for example, of a non-ionic part A, a hydrocarbon chain, and an ionizable part B which may be, for instance, polyacrylic acid, polyphosphoric acid, or sulfonated polystyrene. If a monomer is chosen as solvent S in which A is soluble and B is insoluble, the relationships will resemble those in non-ionic heteropolymers. An example is a soap molecule, consisting of a long fat-soluble chain – even if this is relatively short, compared with the parts of non-ionic copolymers – in which the ionized part is confined to a single group, *i.e.* the carboxyl group.

Interesting results were obtained by combination of the potassium salt of 10-(*p*-ethylphenyl)undecanoic acid with styrene [8,9]. The styrene was added to the soap at 15 °C until saturation was reached. A band structure, made up of the carboxyl groups, was obtained (Fig. 4).

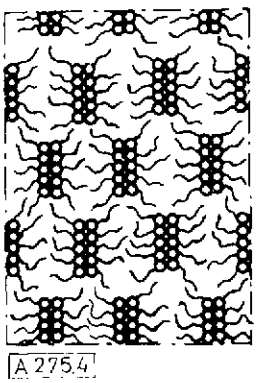

Fig. 4. Band structure of a soap.
o carboxyl group
——— hydrocarbon residue.

The intervening space was taken up by the hydrocarbon chains and the styrene. This structure persists after polymerization of the styrene, as is shown by its X-ray diagram (Fig. 4). The product is white and intensely hygroscopic.

4. Conclusions

Two types of heteropolymers can be distinguished, *viz.* isotropic heteropolymers, *i.e.* homopolymers in which a multiplicity of insoluble small nuclei are included, and anisotropic or organized heteropolymers with visible micro-ranges which possess sub-microscopic layer or cylindrical structures. The structures of the compounds investigated were completely stable.

The method discussed above makes it possible to prepare solid high molecular-weight polymers in which particles are dispersed, the material, shape, size, and concentration of the dispersate being variable within wide limits. Heteropolymers with anisotropic lamellar or cylindrical structures are distinguishable by their dielectric and optical properties. It would be a great advance if it became possible to enlarge the zones of uniform structure, by analogy to seeding of single crystals. Furthermore, the construction of organized polymers with an "insoluble" ionized phase might result in electrolytic condensers or in amplifiers with special characteristics. Beyond that, the construction of very thin threads or films or of porous substances might be conceivable.

Heteropolymers might perhaps also be used as the basis for explosives or solid propellants.

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[6] *Ch. Sadron*, Chimie Pure et Appliquée *4*, 347 (1962).

[7] *G. Finaz, A. Skoulios*, and *Ch. Sadron*, C. R. hebd. Séances Acad. Sci. *253*, 265 (1961).

[8] *F. Husson, J. Herz*, and *V. Luzzati*, C. R. hebd. Séances Acad. Sci. *252*, 3290 (1961).

[9] *J. Herz, F. Husson*, and *V. Luzzati*, C. R. hebd. Séances Acad. Sci. *252*, 3462 (1961).

Solid-State Reactions [*]

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In the following, solid-state reactions between ionic crystals are described. The vast field of powder reactions will not be discussed, since various parameters such as particle size distribution and packing density are difficult to determine exactly. The result of this is, that it is almost impossible to establish the mechanisms of solid-state powder reactions unambiguously and derive general expressions for reaction rates.

1. Introduction

More than thirty years ago, *Schottky* and *Wagner* [1,2] studied the basic principles of defects in ionic crystals, and their concept also proved useful for an understanding of solid-state reactions of ionic crystals. They were able to show that in binary compounds which are in a state of thermodynamic equilibrium with only small deviations from stochiometry, the concentrations of point defects are given functions of the independent thermodynamic variables, *i.e.* temperature, pressure, and the activities of the individual constituents. In the following years, the concept of the different types of disorder has been extensively elaborated [3, 4]. Since ionic crystals appear to be electroneutral, and defects generally have either a positive or a negative electrical charge with respect to the ideal neutral lattice, we may conclude that in ionic crystals there are at least two different kinds of defects, which are oppositely charged. It can be assumed further that the energies of formation of different point defects differ sufficiently. Since defect concentrations depend exponentially at a given temperature upon these energies of formation, one can expect that frequently two sorts of point defects predominate. These two sorts of defects characterize the type of disorder.

If temperatures are high enough, mass transport in solids is controlled almost exclusively by point defects. According to *Wagner* [5], cations are responsible for the mass transport during a reaction between solid oxides, if a compact reaction product separates the reactants from each other. Working on this assumption, transport equations can be derived which are governed by concentrations and mobilities of defects in the reaction product, and by driving forces, represented by the free energy of formation of the reaction product from the reactants.

Defect concentrations in ionic crystals depend on the thermodynamic activity of the constituents. The average value of the concentration of defects in reaction layers therefore depends upon the type of disorder of the reaction product. For a theoretical calculation of reaction rates, it is therefore necessary to have information about the type of disorder.

2. Transport in Ionic Crystals

a) Defects

As stated above, mass transport in ionic crystals is essentially governed by migration of point defects. It is therefore useful to consider in some detail the different types of disorder, characterized by the two kinds of defects which have the highest concentrations. These concentrations are interrelated by the condition of electroneutrality.

Even in binary crystals, a number of possible types of disorder can be expected. Examples are: Frenkel type of disorder, in which vacancies in the cation sublattice are balanced by the same number of interstitial cations (AgBr); Schottky type of disorder with equivalent concentrations of cation and anion vacancies (NaCl); and disorder such as is found for $Fe_{1-x}O$ (wüstite), in which vacancies in the cation sublattice are compensated by defect electrons in the form of Fe^{3+} ions.

For ternary and higher ionic crystals, the number of possible types of disorder is substantially greater than for binary crystals, especially if structurally nonequivalent interstitial sites occur. However, it is in principle always possible to determine ionic disorder types by measuring physical properties related to point defects as a function of the independent thermodynamic variables [6].

b) Mobility

If point defects in crystals are mobile, ions and/or electrons can be transported. Mobility is defined as the mean stationary velocity under the action of a unit force. It can be shown that the self-diffusion coefficient of an ion is – beside constant factors – essentially the product of concentration times mobility of those defects that bring about the corresponding self-diffusion. It is found that the self-diffusion coefficient varies ex-

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[1] *C. Wagner* and *W. Schottky*, Z. physik. Chem., Abt. B *11*, 113 (1930).

[2] *C. Wagner*, Z. physik. Chem., Abt. B, *21*, 25 (1933).

[3] *W. Schottky*, Z. physik. Chem., Abt. B, *29*, 335 (1935).

[4] *W. Jost* and *G. Nehlep*, Z. physik. Chem., Abt. B, *32*, 1 (1936).

[5] *C. Wagner*, Z. physik. Chem., Abt. B, *34*, 309 (1936).

[6] *H. Schmalzried* and *C. Wagner*, Z. physik. Chem. N.F. *31*, 198 (1962).

ponentially with temperature. Since defect concentrations also exhibit an exponential temperature dependence, the same must hold for the mobility.

This situation can be interpreted by assuming [7] that before an elementary jump, the ion vibrates in its potential well according to its average kinetic energy kT. The probability of exceeding the energy barrier ε for passage to the next equivalent vacant site (vacancy diffusion) or interstitial site (interstitial diffusion) corresponds to the Boltzmann factor $\exp(-\varepsilon/kT)$. This model of an elementary diffusion step is considerably oversimplified with regard to the fact that the diffusing ion and its nearest neighbors are part of the vibrational system of the whole crystal, which implies that ε cannot be a simple parameter [8].

Neither mobility nor the energy of formation of defects in ionic crystals can be predicted from theoretical considerations with fair accuracy. Experiments generally do not yield information on defect concentration and mobilities separately. If information on these individual quantities is needed, experimental tricks such as doping or quenching the equilibrium defect concentration are to be applied [9].

c) Driving Forces

It is known from irreversible thermodynamics [10] that, within wide limits, the amount of species transported is proportional to properly defined driving forces. Because of the small reaction rates in the solid state, one can regard the reacting system as being isothermal. For this case, the flux of ions in the reaction product is proportional to the gradient of their electrochemical potential. Furthermore, since the condition of electroneutrality interrelates the fluxes of the different kinds of diffusing ions, their electrochemical potential can be expressed in terms of the chemical potential of the reactants, which is measurable.

If thermodynamic equilibrium is established at the phase boundaries of the reaction layer, and this is true if the thickness Δx of the layer is not too thin, and if the potential within the layer varies linearly with the distance from the phase boundary, then the driving force behind the ion diffusion is equal to the standard free energy of formation ΔG° of the reaction product divided by the thickness Δx.

3. Examples of Solid State Reactions

a) General

The mainly applied method of preparing refractory compounds is by reaction in the solid state. Compounds prepared in this way include technically most important materials such as spinels, ferrites, or titanates. On the basis of experimental data and crystal chemistry, *C. Wagner* [5] proposed counterdiffusion of cations in the reaction layer for the mechanism of spinel formation. From this he derived a phenomenological theory of solid-state reactions. In the following, this theory is extended to anion migration in the reaction product, and after that the formation of oxides, halides, and sulfides in the solid state is discussed by way of characteristic examples.

In Figure 1, the different possible mechanisms are given for the hypothetical reaction $AX + BX = ABX_2$, where A and B are the cations and X is the common anion. It is assumed that single crystals AX and BX react to form a compact product ABX_2, which separates the reactants from each other.

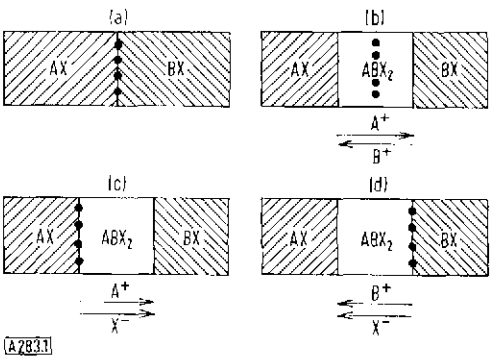

Fig. 1. Possible mechanisms of the reaction $AX + BX \rightarrow ABX_2$
a) reactants
b) $2\,AX + B^+ \rightarrow ABX_2 + A^+$
$2\,BX + A^+ \rightarrow ABX_2 + B^+$
c) $BX + A^+ + X^- \rightarrow ABX_2$
d) $AX + B^+ + X^- \rightarrow ABX_2$
● cross section of a wire marker.

As long as electronic conduction in ABX_2 is negligible the reaction can only proceed by ion migration. Figure 1 shows the three limiting cases. The condition of electroneutrality requires a coupling of the ionic fluxes, and the rate of reaction is determined essentially by the ion with a self-diffusion coefficient which has values between the coefficients of the other two ions. If, however, the transport numbers of electrons or defect electrons cannot be neglected, it seems possible that part of the mass transport goes via the gaseous atmosphere, while electrons or defect electrons diffuse through the reaction layer.

If in the quasibinary system AX–BX several intermediate compounds exist, it is essentially the product of the mobility of the rate-determining ion times the gradient of the chemical potential which determines the thickness of the different phases in the reaction layer. Since these products frequently differ significantly from one another, it is generally found that even when several compounds are formed, one phase predominates.

For the investigation of reaction mechanisms, inert markers may be interposed between the reactants AX and BX before the reaction begins. From the position of the markers after the reaction, one obtains information on either transport of AX (Fig. 1c) in one direction, or on counter-diffusion of the cations (Fig. 1b). However, a final conclusion about the reaction mechanism is possible only by comparing experimental and calculated reaction rates; since there is always the possibility of

[7] *C. Zener:* Imperfections in Nearly Perfect Crystals. Wiley, New York 1952.

[8] *St. A. Rice*, Physic. Rev. *112*, 804 (1958).

[9] *E. Koch* and *C. Wagner*, Z. physik. Chem., Abt. B, *38*, 295 (1938).

[10] *S. R. de Groot:* Thermodynamics of Irreversible Processes. North Holland Publishing Company, Amsterdam 1962.

transport via the surrounding atmosphere. To this end, the flux j_i of ions of sort i per second and unit area is calculated according to Section 2 as

$$j_i = \frac{D_i c_i}{RT} \cdot \operatorname{grad} \eta_i \qquad (a)$$

where j_i is given in moles/cm²/sec, D_i is the self-diffusion coefficient, c_i the concentration, and η_i the electrochemical potential in the reaction layer.

After taking into account the condition of electroneutrality and effecting several rearrangements, equation (a) yields the parabolic rate law in the form:

$$\Delta x^2 = 2 \bar{k} \bar{v} t \qquad (b)$$

where $\bar{k}$ is the so-called rational reaction constant and $\bar{v}$ is the increase in volume of the reaction product on passage of one mole of ions of sort i. Δx is again the thickness of the reaction layer. The reaction constant $\bar{k}$ can be calculated from the standard free energy of formation of the reaction product and the average value of transport coefficients, which are given either in the form of the self-diffusion coefficient $\bar{D}_i$ or in the form of the partial electrical conductivity $\bar{\sigma}_i$ of the ion i in the reaction product. If, for example, $\bar{D}_X \gg \bar{D}_A \gg \bar{D}_B$, $\bar{k}$ becomes

$$\bar{k} = c_A \bar{D}_A \frac{\Delta G^\circ}{RT} \qquad (c)$$

In order to calculate the average value of the transport coefficient of ion A, however, the type of disorder of the reaction product should be known.

b) Reaction between Solid Oxides (Spinel Formation)

As an example of spinel formation by solid-state reactions, the reaction between a single crystal of rutile and coarse crystals of cobalt oxide may be considered [11]. According to equation (d), cobalt titanate is the essential reaction product:

$$2\,CoO + TiO_2 = Co_2TiO_4 \qquad (d)$$

Experiments with inert markers in a nitrogen atmosphere show, that under this condition, the reaction proceeds by counter-diffusion of the cations (Fig. 2). After the reaction has occurred, the markers (thin platinum wires) are found in the middle of the spinel layer (Fig. 2b). This can readily be explained by the two half-reactions

$$4\,CoO + Ti^{4+} (\leftarrow) = Co_2TiO_4 + 2\,Co^{2+} (\rightarrow) \qquad (e)$$
$$2\,Co^{2+} (\rightarrow) + 2\,TiO_2 = Co_2TiO_4 + Ti^{4+} (\leftarrow)$$

which take place at the corresponding phase boundaries. If spinel formation from CoO and TiO_2 occurs in air instead of nitrogen, the inert markers are found at the Co_2TiO_4/TiO_2 phase boundary (Fig. 2c), indicating that CoO is transported towards this phase boundary.

Since the type of disorder (inverse spinel), the transport number of electrons, the self-diffusion coefficient of cobalt and oxygen in Co_2TiO_4, and the free energy of formation from the single oxides (from emf-measurements at high temperatures) are known, the reaction constant $\bar{k}$ can be calculated on the assumptions that diffusion of Co^{2+} is rate-determining, that electrons migrate in the same direction through the reaction layer, and that there is sufficient oxygen available from the atmosphere at the interface Co_2TiO_4/TiO_2. Experimental and calculated reaction constants are in good agreement (Fig. 3). Since the reaction rate in an oxygen-free atmosphere is considerably smaller than that in the presence of oxygen, it is concluded that counter-diffusion of cations takes place under this condition, and that diffusion of titanium ions becomes rate-determining.

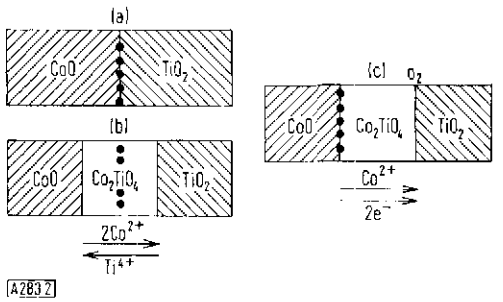

Fig. 2. Mechanism of the reaction $2\,CoO + TiO_2 \rightarrow Co_2TiO_4$.
a) reactants
b) reaction in nitrogen:
$Ti^{4+} + 4\,CoO \rightarrow Co_2TiO_4 + 2\,Co^{2+}$
$2\,TiO_2 + 2\,Co^{2+} \rightarrow Co_2TiO_4 + Ti^{4+}$
c) reaction in air:
$2\,Co^{2+} + 4e^- + TiO_2 + O_2 \rightarrow Co_2TiO_4$
● cross section of a wire marker.

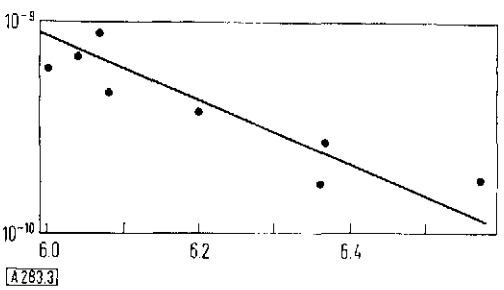

Fig. 3. Dependence of the rate constant of the reaction $2\,CoO + TiO_2 \rightarrow Co_2TiO_4$ (in air) on temperature
Curve: calculated from $D_{Co^{2+}}$. Points: measured values
Ordinate: reaction rate constant [equiv./cm/sec]
Abscissa: $(1/T) \times 10^4$ [1/°K]

c) Reactions between Solid Halides

As an example of solid-state reactions between halides, the reaction $KCl + SrCl_2$ may be considered. The reaction product consists mainly of K_2SrCl_4 [12]. After the reaction, inert markers are always found in or close to the interface K_2SrCl_4/KCl, leading to the conclusion that only KCl is transported in the form of ions through the reaction layer. To test this conclusion, the transport numbers of potassium, strontium, and chlorine were determined by measuring their self-diffusion coefficients, by marker studies, and by emf-measurements. It was found that the transport number of potassium is significantly smaller than that of chlorine and significantly larger than that of strontium, so that diffusion of potassium in K_2SrCl_4 during the reaction should be

[11] *H. Schmalzried*, Z. physik. Chem. N.F. *33*, 111 (1962).

[12] *H. Schmalzried*, Z. physik. Chem. N.F. *33*, 129 (1962).

rate-determining. Since the self-diffusion coefficient of potassium is known from radioactive tracer measurements in K_2SrCl_4, and the driving force behind the reaction could be obtained from an analysis of phase-diagram data and emf-measurements, it is possible to calculate the reaction constant $\bar{k}$. The agreement between the experimental result $\bar{k}_{exp}$ (485 °C) = 6×10^{-12} equiv/cm/sec and the calculated value $\bar{k}_{calc} = 4 \times 10^{-12}$ equiv/cm/sec confirms that the reaction mechanism involves diffusion of potassium and chloride ions in the same direction.

d) Reactions between Solid Sulfides

An example of reactions between solid sulfides was studied by *Rickert* and *Wagner* [13, 14]. From the phase diagram, one can expect formation of the double sulfides $AgSbS_2$ and Ag_3SbS_3 in the quasibinary system Ag_2S–Sb_2S_3. The amounts of these sulfides in the reaction layer, however, are quite different, since the products of the transport coefficients of the rate-determining ions and the potential gradients in the corresponding compounds differ widely. Hence, only the formation of $AgSbS_2$ will be discussed here. Marker studies confirm a reaction mechanism by counter-diffusion of cations (Fig. 4). The reactions occurring at the phase boundaries are given in the legend. From measurements of electrical partial conductivities it can be concluded that the antimony ions are rate-determining. Since, in addition, the free energy of formation

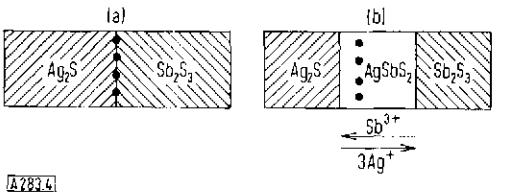

Fig. 4. Mechanism of the reaction $Ag_2S + Sb_2S_3 \rightarrow 2\,AgSbS_2$.
a) reactants
b) $Sb^{3+} + 2\,Ag_2S \rightarrow AgSbS_2 + 3\,Ag^+$
$3\,Ag^+ + 2\,Sb_2S_3 \rightarrow 3\,AgSbS_2 + Sb^{3+}$
● cross section of a wire marker.

is known, it would be possible to calculate the reaction rate, if the self-diffusion coefficient of antimony in $AgSbS_2$ had been measured, and could then have been compared with experimental values. Such a verification is still to be made.

4. Concluding Remarks

Solid-state reactions have been used for many years to produce everyday articles; examples are the cementation of iron and the manufacturing of refractories by the ceramic industry. It is still beyond our knowledge [15] to what extent minerals are formed by solid-state reactions in geological processes.

Another application of reactions between solids is the growing of ternary and higher ionic single crystals. The method seems useful if reactants are available in the form of single crystals, and if the molar volume and structure of the reaction product are not too different from those of the reactants [16].

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[13] *H. Rickert* and *C. Wagner*, Z. Elektrochem. Ber. Bunsenges. physik. Chem. *64*, 793 (1960).

[14] *H. Rickert* and *C. Wagner*, Z. Elektrochem. Ber. Bunsenges. physik. Chem. *66*, 502 (1962).

[15] *R. Jagitsch*, Ark. Mineralog. Geol. *1*, 2 (1949).

[16] *W. Rogalla* and *H. Schmalzried*, unpublished data.

Preparative and Analytical Separation of Organic Compounds by Means of Chromatography on Polyamide

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Dedicated to Prof. Dr. Adolf Butenandt on the occasion of his 60th birthday

Columns of polyamide are well suited for chromatographic separation of numerous organic compounds, especially phenols, carboxylic acids, and aromatic nitro compounds. The method is also useful for isolating naturally occurring compounds on a preparative scale. The affinity of phenols for polyamides is due to the formation of hydrogen bonds to the peptide linkages of the polyamide, while aromatic nitro compounds are retained by means of free amino groups in the polymer. Quinones react irreversibly with the free amino groups of the polyamide. Quinones are not retained by acetylated polyamides although phenols are.

Introduction

Linear polymeric resins with a low degree of cross-linking and built-in binding groups of specific activities may be used as the stationary phase for chromatographic systems of comparatively high capacity. An example of such a system is the group of ion-exchange resins [1], which consist of an inert, high-molecular-weight lattice containing acidic or basic groups. The resins must be capable of swelling. Swelling of the

[1] Review: *F. Helfferich:* Ion Exchangers. MacGraw Hill, New York 1962.

particles permits the substances to be separated to penetrate into the interior of the exchange resin, where they are temporarily retained. Chromatography is thus carried out here on a stationary phase with numerous chemically identical binding centers. At the most, these centers differ slightly in reactivity because of their slightly varying spatial arrangement in the lattice system of the polymer. Nevertheless, they may be considered as equivalent within narrow limits. Thus, ions which have a charge opposite to that of the exchange resin generally become distributed between the interior of the resin and any surrounding buffer solution in a proportion which is only very slightly dependent upon the concentration over wide limits. [2]. This is the prerequisite for allowing the substances to be separated to pass through the column in clear-cut bands even at higher concentrations [3].

In place of acidic or basic centers of affinity, other selectively acting binding groups can be incorporated into the exchange resin. Corresponding resins for selective adsorption of inorganic ions are already well known, *e.g.* polystyrene resins with dipicrylamine groups for potassium ions [4], exchange resins with hydroxamic acid groups for iron ions [5], with mercapto groups for mercury ions [6], or with complexing groups for the ions of some transition metals [7].

Adsorption of Phenols

Exceptionally strong hydrogen bonding occurs between phenolic hydroxyl groups and amide bonds.

The formation of well-defined adducts, *e.g.* between phenol and urea in a proportion of 2:1 [8] or between phenol and diketopiperazine [9], is based upon the existence of these strong secondary valence bonds. Additional evidence for the presence of these bonds was obtained by means of infrared spectra [10] and from measurement of the dielectric constants [11] of phenol/amide mixtures. On the basis of infrared data, *Flett* [12] determined the energy of the hydrogen bond between phenol and dimethylformamide to be 6.4 kcal/mole. Among other things, hydrogen bonding between phenols and the peptide linkages of proteins is believed to account for the affinity of substantive dyes towards wool [13, 14]. Furthermore, these bonds play an important role in the tanning of hides with vegetable tannins [15]. The pronounced affinity of phenols toward peptide bonds has long been utilized for separating proteins from non-proteins by extraction with phenols [16]. Finally, solvent systems containing phenol are suitable for separating peptides by paper chromatography. According to the results of *Grassmann* and *Deffner* [17], the affinity of peptides towards phenol increases with the chain length of the peptide.

On the basis of these findings, polymers containing peptide bonds should be suitable for separating phenolic substances. Commercially available polyamides are either of the Perlon type (polycaprolactam) or nylon type (polyhexamethylenediamine adipate). Because these compounds are cross-linked by means of hydrogen bridges, they are sufficiently insoluble in most solvents but are still capable of swelling. As early as 1942, *Huggins* [18] and *Flory* [19] derived a thermodynamic relationship for the adsorption of substances by high polymers capable of swelling, including the adsorption of phenols on polyamides.

The adsorption of phenol from aqueous solution by polycaprolactam follows a linear distribution function over a wide range of concentrations [20] (up to 0.2 M phenol); see Fig. 1.

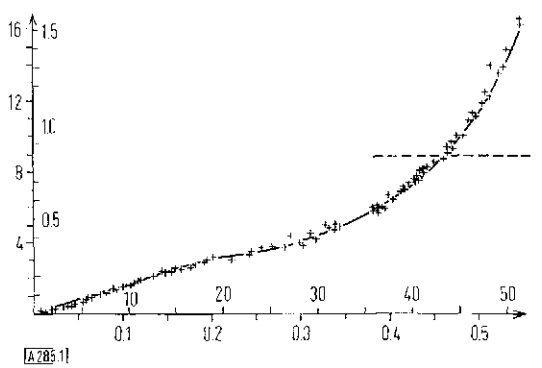


Fig. 1. Distribution of phenol between polycaprolactam and water [20]. The dashed line indicates the uptake of 1 mole phenol/mole amide bond.
Ordinate: phenol concentration in polycaprolactam (left-hand scale [mmoles/g], right-hand scale [g/g].
Abscissa: phenol concentration in water (upper scale [mg/ml], lower scale [mmoles/ml]).

Only at higher concentrations is the sorption isotherm bent downward to some extent, this being indicative of partial saturation. As the phenol concentration increases further, the isotherm curves upward, and the polyamide swells, softens,

[2] See, for example, *T. R. E. Kressman* and *I. A. Kitchener*, J. chem. Soc. (London) *1949*, 1190, 1201, 1208, 1211.

[3] *A. J. P. Martin* and *R. L. M. Synge*, Biochem. J. *35*, 1358 (1941).

[4] *A. Skogseid*, Ph. D. thesis, University of Oslo 1948; US.-Pat. 2592350 (1952), Norsk Hydro-Elektrisk kv., inventor: *A. Skogseid*; see also [1].

[5] *J. P. Cornaz* and *H. Deuel*, Experientia *10*, 137 (1954).

[6] US.-Pat. 2418497 (1947), E. I. DuPont de Nemours, inventor: *W. I. Burke*; see also [1]; *H. P. Gregor, D. Dolar*, and *G. K. Hoeschele*, J. Amer. chem. Soc. *77*, 3675 (1955).

[7] *H. P. Gregor, M. Taifer, L. Citarel*, and *E. I. Becker*, Ind. Engng. Chem. *44*, 2834 (1952); *E. Jenckel* and *H. V. Lillin*, Kolloid-Z. *146*, 159 (1956); *E. Blasius* and *G. Olbrich*, Z. analyt. Chem. *151*, 81 (1956).

[8] *H. Eckenroth*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. (3) *24*, 623 (1886); see also *A. Baeyer* and *V. Villiger*, Ber. dtsch. chem. Ges. *35*, 1201 (1902); *K. Freudenberg*, Collegium *616*, 353 (1921).

[9] *P. Pfeiffer*: Organische Molekülverbindungen. Thieme, Stuttgart 1927; *P. Pfeiffer, O. Angern, L. Wang, R. Seydel*, and *K. Quehl*, J. prakt. Chem. *126*, 97 (1930).

[10] *C. G. Cannon*, Mikrochim. Acta *1955*, 555.

[11] *C. H. Giles, T. J. Rose*, and *D. G. M. Vallance*, J. chem. Soc. (London) *1952*, 3799; *F. M. Arshid, C. H. Giles, S. K. Jain*, and *A. S. A. Hassan*, J. chem. Soc. (London) *1956*, 72.

[12] *M. St. C. Flett*, J. Soc. Dyers Colourists *68*, 59 (1952).

[13] *J. Steinhardt, C. H. Fugitt*, and *M. Harris*, J. Res. nat. Bur. Standards *25*, 519 (1940); *26*, 293 (1941); *30*, 123 (1943); *J. B. Spackman* and *E. Stott*, Trans. Faraday Soc. *31*,1425 (1935).

[14] For the development of non-ionogenic dyestuffs see *G. Otto*, Leder *4*, 1 (1953).

[15] *W. Grassmann, H. Endres, M. Oppelt*, and *H. El Sissi*, Leder *10*, 149 (1959), and further references cited therein.

[16] Cf. *O. Westphal, O. Lüderitz*, and *F. Bister*, Z. Naturforsch. *7b*, 148 (1952).

[17] *W. Grassmann* and *G. Deffner*, Hoppe-Seylers Z. physiol. Chem. *293*, 89 (1953).

[18] *M. L. Huggins*, Ann. N. Y. Acad. Sci. *43*, 1 (1942).

[19] *P. J. Flory*, J. chem. Physics *10*, 51 (1942).

[20] *W. Grassmann, H. Hörmann*, and *A. Hartl*, Makromolekulare Chem. *21*, 37 (1956).

and eventually dissolves completely. The phenol adsorption is completely reversible. The phenol may be washed out of the polycaprolactam with water even after the phenol has been bonded to the polyamide for some time [20].

The curve for the distribution of phenol between polycaprolactam and water remains linear until approximately one-third of the peptide bond of the polyamide has become saturated (Fig. 1). In this range, the distribution coefficient of the phenol, based on the relative weights of water and polycaprolactam, is 12.2. *Forward* and *Palmer* [21] found a value of 14.3 for water/poly(hexamethylenediamine adipate). It is probable that this linear relationship applies only to the adsorption of phenol within the noncrystalline range of the polyamide.

On tempering for an extended period at 200–230 °C, nylon becomes more crystalline (as shown by X-ray patterns), and the adsorption of phenol from a 2% aqueous solution decreases [21]. The free energy of transfer of the phenol from the aqueous phase into the nylon phase was determined to be 4 kcal/mole from the dependence of the distribution coefficient.

Chromatography of Phenols

The fact that, in these systems, the distribution coefficient remains constant up to comparatively high concentrations of phenol forms an ideal basis for chromatographic separations. Initial experiments in this connection were carried out by *Carelli* et al. [22]. They utilized frontal analysis – a method that is little used nowadays – to separate a mixture of three isomeric derivatives of xylenol. It was further shown by *Grassmann*, *Hörmann*, and *Hartl* [20] that some phenols may be separated completely by elution chromatography. Both research groups pointed out that the capacity of polyamide columns is extraordinarily large compared to other chromatographic systems. It should thus be possible to separate substances on a semipreparative scale. In the experiments of *Grassmann* et al., it was shown, for example, that amounts of up to 0.33 mmole of single phenolic substances could be applied to a small column (15 cm long, 0.9 cm in diameter) containing 3 g of Perlon powder, whereas with the usual methods of adsorption and distribution chromatography, only a few μmoles could be applied to a column of equal size without overloading it. These advantages result from the fact that the distribution coefficient remains constant over a wide range of concentrations.

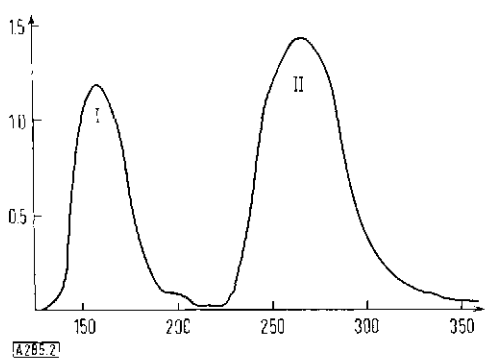


Fig. 2. Separation of a mixture of 20 mg phenol (I) and 40 mg m-cresol (II) on polycaprolactam.

Elution solvent: Water. Column 48 cm long, 1.3 cm diameter.

Ordinate: Extinction at 546 mμ after the color reaction with Folin-Denis reagent.

Abscissa: Number of fractions of 1.45 ml each.

Figure 2 illustrates the separation of a mixture of 20 mg of phenol and 40 mg of *m*-cresol on a column (48 cm long, 1.3 cm in diameter) filled with poly-ε-caprolactam, using water as eluant. Despite the relatively large quantities of mixture applied, both compounds emerge from the column well separated into symmetric bands.

Polycaprolactam, *e.g.* Ultramid BM 228 (0.2 mm mesh), from the Badische Anilin- und Sodafabrik, is especially well suited for separations by column chromatography. It should be free of monomer, since this travels through the column as molecular complexes together with the substances to be separated. Any monomer present can be removed by washing the polyamide in the column with dimethylformamide or a mixture of dimethylformamide, glacial acetic acid, water, and ethanol in proportions of 5:10:30:20. The phenols in the eluate are most conveniently determined by means of the color reaction of *Folin* and *Denis* [23].

Table 1. R_F-Values of some lower phenols on polycaprolactam

	Solvent		
	Water	20% Acetone	50% Ethanol
Phenol	0.21	0.39	0.66
o-Cresol	0.24	0.42	0.69
m-Cresol	0.115	0.25	0.61
Pyrocatechol	0.30	0.46	0.62
Resorcinol	0.16	0.40	0.58
Hydroquinone	0.18	0.39	0.55
Pyrogallol	0.36	0.53	0.66
Phloroglucinol	0.07	0.20	0.49

Table 1 shows the R_F values of some lower phenols. The affinity towards polycaprolactam increases in the sequence phenol, resorcinol, phloroglucinol, while a decrease is observed in the sequence phenol, pyrocatechol, pyrogallol. Hydroquinone behaves similarly to resorcinol. A second or third hydroxyl group on the aromatic nucleus increases the adherence of the substance to the polyamide, provided these hydroxyl groups are in either the *meta*- or the *para*-position. However, another hydroxyl group in the *ortho*-position tends to accelerate the rate of travel. Both hydroxy groups of resorcinol or hydroquinone are apparently capable of interacting simultaneously with different peptide bonds of the polyamide. This enables these compounds to be retained more tightly than phenol. The hydroxyl groups of pyrocatechol, however, are forced to compete for the same peptide group. The second hydroxyl group thus reinforces the affinity toward most aqueous eluants and therefore increases the rate of travel. In addition, partial saturation by intra-

[21] *M. V. Forward* and *H. J. Palmer*, J. Textile Inst. *45*, T 510 (1954).

[22] *V. Carelli*, *A. M. Liquori*, and *A. Mele*, Nature (London) *176* 70 (1955).

[23] *O. Folin* and *A. Denis*, J. biol. Chemistry *22*, 305 (1915).

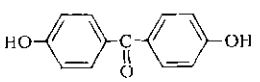
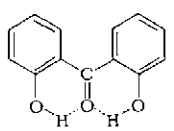
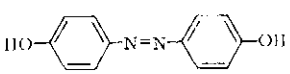
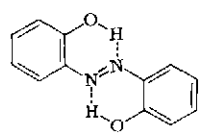
molecular hydrogen bonding must be taken into consideration. Hydrophobic groups, particularly large aromatic nuclei, decrease the rate of travel [15]. Phenols with several nuclei and many hydroxyl groups are retained relatively strongly by polyamide, except when the hydroxyl groups are saturated by intramolecular hydrogen bonding [15,24,25]; see Tables 2 and 3. It is

Table 2. Decrease of R_F-values of phenols with increasing aromatic system in the molecule. Solvent: 50 % methanol

Phenol	0.63	Hydroquinone	0.57
α-Naphthol	0.28	4,4'-Dihydroxydiphenyl	0.15
β-Naphthol	0.28	Resorcinol	0.58
2-Hydroxydiphenyl	0.22	2,4-Dihydroxydiphenylmethane	0.16
4-Hydroxydiphenyl	0.21		

peculiar that tyrosine is not retained by polycaprolactam [20]. This anomalous behavior is frequently observed in compounds with zwitterionic properties (see below).

Table 3. Influence of intramolecular hydrogen bonding upon the affinity towards polyamide [24]

	R_F-values in			
	Methanol/water (1:1)	Acetone/water (1:1)	Methanol	Acetone
 4,4'-Dihydroxybenzophenone	0.16	0.62	0.76	0.78
 2,2'-Dihydroxybenzophenone	0.27	0.77	0.95	0.95
 4,4'-Dihydroxyazobenzene	0.18	0.51	0.72	0.78
 2,2'-Dihydroxyazobenzene	0.23	0.61	0.86	0.88

The eluting power increases in the order: water, methanol, acetone, dimethylformamide. These solvents progressively accelerate the rate of elution since they also form hydrogen bonds and thus may replace the phenol on the polyamide. Phenols are eluted instantaneously with dilute sodium hydroxide, since phenoxide ions are no longer capable of forming hydrogen bonds with polyamides.

[24] *H. Endres*, Z. analyt. Chem. *181*, 331 (1961).

[25] Compare the results in other chromatographic systems: *H. Hoyer*, Chem. Ber. *86*, 1016 (1953); *89*, 146 (1956); *A. Küntzel, H. Rosenbusch*, and *H. El Sissi*, Leder *10*, 133 (1959).

Examples of Application

Naturally Occurring Compounds

Chromatography of phenolic compounds on polyamides [26] has already been frequently used for the purification and elucidation of the structures of naturally occurring compounds such as spruce-bark tannins [27,28], in the isolation of two hydroxystilbenes from *Eucalyptus wandoo* [29], sumac tannins [30], or several aromatic hydroxyacids from *Acacia arabica* [31].

The behavior of vegetable tannin precursors and other polyhydroxyphenols towards polyamide may be considered a model for essential phenomena which occur during the tanning process [15]. It confirms the theory that, among other things, hydrogen bonding between phenolic hydroxyl groups and the peptide bonds of the hide is responsible for the bonding of tannin. The adsorption of some polyhydroxyphenols by polyamides appears to run parallel to their tanning effect on hides [15, 32, 33].

Hörhammer and *Wagner* [34–36] separated the components of several plant extracts of pharmacological importance. As an example, mention should be made of the separation of the anthoxanthins from the blossoms of the linden tree [35], from which nine components were obtained in crystalline form (mostly glycosides of quercetin and kaempferol). Other authors recovered uniform compounds [39] from *Helichrysum arenarium* [37] and elder blossom extracts [38]. *O. Th. Schmidt* [40] separated

[26] German Pat. 106383 (27. Apr. 1957), Max-Planck-Institut für Eiweiß- und Lederforschung, inventors: *W. Grassmann, H. Hörmann*, and *H. Endres*.

[27] *W. Grassmann, H. Endres, W. Pauckner*, and *H. Mathes*, Chem. Ber. *90*, 1125 (1957); *W. Grassmann, H. Endres*, and *W. Pauckner*, Chem. Ber. *91*, 134 (1958).

[28] For the separation of the tannin glucoside mixture see *H. Endres* and *K. Merkle*, Chem. Ber. *94*, 431 (1961).

[29] *D. E. Hathway* and *J. W. T. Seakins*, Biochem. J. *72*, 369 (1959).

[30] *R. D. Haworth*, Lecture at the Symposium on Current Chemical Research on Plant Phenolics, April 22nd, 1960, Egham, Surrey (England).

[31] *H. Endres* and *M. Hilal*, Phytochemistry, in the press.

[32] *H. Endres*, Leder *12*, 294 (1961).

[33] Compare the chromatography of homologous pyrocatechol condensation products (*Z. Kotásek, J. Strachota, M. Vavrová*, and *J. Spičková*, Chem. Prumysl *10*, 321 (1960)) and of aromatic syntans on polyamide [*F. Stather, G. Reich*, and *S. Wünsch*, Gesammelte Abh. dtsch. Lederinst. Freiberg/Sa. *15*, 111 (1959)].

[34] *L. Hörhammer, H. Wagner*, and *W. Leeb*, Naturwissenschaften *44*, 513 (1957); *L. Hörhammer, H. Wagner*, and *H. J. Lene*, Dtsch. Apotheker-Ztg. *99*, 1043 (1959); *L. Hörhammer, H. Wagner*, and *H. Grasmaier*, Naturwissenschaften *45*, 388 (1958); *L. Hörhammer, H. Wagner, J. Izquierdo-Sorli*, and *H. Endres*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *291/63*, 269 (1958); *L. Hörhammer, H. Wagner*, and *O. Föcking*, Pharmaz. Ztg. *104*, 1183 (1959).

[35] *L. Hörhammer, L. Stich*, and *H. Wagner*, Naturwissenschaften *46*, 358 (1959).

[36] Review: *L. Hörhammer* and *H. Wagner*, Pharmaz. Ztg. *104*, 783 (1959).

[37] *J. Vrkoc, V. Herout*, and *F. Sorm*, Collect. czechoslov. chem. Commun. *24*, 3938 (1958).

[38] *J. Davidek*, Nature (London) *189*, 487 (1961); Nahrung *4*, 660 (1960); Z. Lebensmittel-Unters. u. -Forsch. *113*, 272 (1960).

[39] Chromatography of chalkones and flavones: *R. Neu*, Nature (London) *182*, 660 (1958); Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *293*, 169 (1959).

[40] *O. Th. Schmidt* and *W. Schönleben*, Z. Naturforsch. *12b*, 262 (1957); *O. Th. Schmidt, P. Becher*, and *M. Hübner*, Chem. Ber. *93*, 1296 (1960); see also *R. G. Petersen* and *M. A. Joslyn*, Food Res. *25*, 429 (1960).

the dye substances of the beetroot; using polyamide, *Weinges* [41] obtained a preparative-scale separation of the substances contained in the berries of *Crataegus oxyacantha*. An important advantage of polyamide chromatography in connection with the isolation of all these compounds in pure form is the clean separation from the tannins contained in these extracts, which heretofore have made crystallization so difficut [36]. One application of industrial interest is the removal of the tannins from beer, which cause it to be turbid, by filtration through a layer of nylon powder [42].

Butenandt et al. [43] successfully applied polyamide chromatography for separating ommochromes, the insect eye pigments, which have a phenoxazine skeleton. It was possible to separate xanthommatine, rhodommatine, and ommatine D on polycaprolactam (Ultramid MB2 K 228 from the BASF), the first compound being eluted with a 0.066 molar phosphate buffer, while the latter two were then eluted with 1 M or 2 M pyridine/acetic acid buffer at pH 6.5 and 7.0, respectively. The high adsorption capacity of the polycaprolactam powder permits separation of up to one gram of crude ommatine on a column 60 cm long and 6 cm in diameter. *Brockmann* et al. [44] separated 200 mg of a mixture of ε-rhodomycinone and ε-isorhodomycinone on polyamide columns 60 cm long and 4.5 cm in diameter with methanol/7 % aqueous pyridine (2:1) [45].

By means of thin-layer and paper chromatography on polyamide, it also proved possible to separate phenolic substances of naturally occurring compounds. *Hörhammer* et al. [46] worked out a procedure which is useful, for example, for differentiating some types of glucosides of flavonols [47]. *Martin* et al. [48] impregnated chromatographic paper with a solution of poly(hexamethylene adipamide), *i.e.* nylon 66, in formic acid. With this, they separated some lower phenols, employing a mixture of 10 % aqueous acetic acid or 7 % acetic acid in cyclohexane as developer. Sharp spots were obtained only when the paper was impregnated with more than 7 % (optimum 10–15 %) of its weight of polyamide [49].

Carboxylic Acids

The carboxyl group also has an affinity towards polycaprolactam [22,50] (Table 4). The affinity is only slight with monocarboxylic acids. However, dicarboxylic acids and aromatic carboxylic acids adhere better,

Table 4. R_F-Values of some carboxylic and sulfonic acids on polycaprolactam

	Eluant		
	Water	50 % Methanol	50 % Acetone
Propionic acid	1.00	1.00	–
Butyric acid	0.95	1.00	–
Caproic acid	0.92	0.96	–
Succinic acid	0.86	1.00	0.96
Glutaric acid	0.71	0.88	0.74
Adipic acid	0.67	0.83	0.69
Phenylacetic acid	–	0.67	0.71
Benzoic acid	–	0.56	0.65
α-Naphthoic acid	–	0.27	0.32
Salicylic acid	–	0.60	0.58
p-Hydroxybenzoic acid	–	0.34	0.44
Benzenesulfonic acid	0.35	0.43	–
p-Toluenesulfonic acid	0.20	0.48	–
Naphthalene-β-sulfonic acid	0.08	0.15	–
Benzenesulfonamide	–	0.82	–
4-Sulfonamido-2,4'-diamino-azobenzene (Prontosil Rubrum)	–	0.18	0.67

particularly when the aromatic portion of the molecule is large (*e.g.* naphthoic acid [50]). The difference between salicylic acid and *p*-hydroxybenzoic acid can be easily explained by the screening effect of the *ortho*-hydroxyl group which causes intramolecular hydrogen bonding. Aromatic sulfonic acids and their amides are also retained by polyamide.

Aromatic Nitro Compounds

Pronounced adherence to polyamide is found with numerous nitro compounds [50]: the higher nitrated derivatives in particular are bound very tightly. Although they can be eluted with such strong solvents as formamide, dimethylformamide, or pyridine, they travel in broad, poorly defined zones. In contrast, sharp fractions are obtained if a mixture of dimethylformamide, glacial acetic acid, water, and ethanol is used for elution [51,52].

The adherence of aromatic nitro compounds increases in the order nitrobenzene < 1,3-dinitrobenzene < 1,3,5-trinitrobenzene. Substituents with a free electron pair in the position *para* to the nitrogen lower the affinity (Table 5).

Exceptions are noted, *e.g.* when a substituent cannot assume a position coplanar with the aromatic nucleus (as in the case of 2,4-dinitro-*N*,*N*-dimethylaniline [53]) or when it contributes additional affinity to the polyamide, for instance, by forming hydrogen bonds (2,4-dinitrophenol or 2,4-dinitroaniline) [52]. Because of steric factors, the NH groups in both 2,4-dinitro-*N*-methylaniline and 2,4-dinitroacetanilide can form an intramolecular hydrogen bond only to the *ortho*-nitro group and are thus excluded from participation in polyamide bonding [53]. Trinitrobenzene and other higher nitrated aromatic compounds adhere very strongly to

[41] *K. Weinges*, Chem. Ber. *94*, 3032 (1961).

[42] *G. Harris* and *R. W. Ricketts*, J. Inst. Brewing *1959*, 41; *1960*, 313.

[43] *A. Butenandt*, *E. Biekert*, *H. Kübler*, and *B. Linzen*, Hoppe-Seylers Z. physiol. Chem. *319*, 238 (1960).

[44] *H. Brockmann* and *H. Brockmann Jr.*, Chem. Ber. *94*, 2681 (1961).

[45] Chromatography of other antibiotics containing phenolic hydroxyl groups: German Pat. 1116866 (Oct. 8th, 1960), Arzneimittelwerk Dresden, inventors: *H. Tönjes* and *H. Pötter*.

[46] *L. Hörhammer*, *H. Wagner*, and *W. Leeb*, Ph.D. thesis *W. Leeb*, Univers. München 1959.

[47] *K. Egger*, Z. analyt. Chem. *182*, 161 (1961).

[48] *W. N. Martin* and *R. M. Husband*, Analytic. Chem. *33*, 840 (1961).

[49] Cf. the separation of furochromes by *H. Friedrich* u. *C. Horstmann*, Pharmazie *16*, 319 (1961).

[50] *H. Endres*, *W. Grassmann*, and *M. Oppelt*, Hoppe-Seylers Z. physiol. Chem. *317*, 21 (1959).

[51] *H. Hörmann* and *H. v. Portatius*, Hoppe-Seylers Z. physiol. Chem. *315*, 141 (1959).

[52] *W. Grassmann*, *H. Hörmann*, and *H. v. Portatius*, Hoppe-Seylers Z. physiol. Chem. *321*, 120 (1960).

Table 5. R_F-Values of some nitro compounds on polycaprolactam [52]

Dimethylformamide/glacial acetic acid/water/ethanol (5:10:30:20)

Nitrobenzene	0.69
1,2-Dinitrobenzene	0.92
1,3-Dinitrobenzene	0.60
3-Nitro-*N*,*N*-dimethylaniline	0.80
4-Nitro-*N*,*N*-dimethylaniline	0.80
2,4-Dinitro-*N*,*N*-dimethylaniline	0.63
2,4-Dinitrothioanisole	0.92
2,4-Dinitro-*N*-methylaniline	0.92
2,4-Dinitroacetanilide	0.71
2,4-Dinitroaniline	0.43
2,4-Dinitrophenol	0.42

Polyethyleneglycol/formamide/formic acid/dimethylformamide/acetic acid/water/ethanol (40:20:15:30:50:35:50)

3,5-Dinitrosalicylic acid	0.56	Picrolonic acid	0.39
Picric acid	0.55	1,3,5-Trinitrobenzene	0.39
Martius yellow	0.48	2,4-Dinitro-1-naphthol-7-sulfonic acid	0.21
Styphnic acid	0.46	®Amidoblack 10B	0.00

polyamide and require complicated solvent mixtures for sharp and clean elution [52] (Table 5).

N-(2,4-Dinitrophenyl)amino acids, which are formed in the determination of the amino end groups of peptides and proteins using dinitrofluorobenzene, may also be separated in columns filled with polyamides [54]. *Steuerle* and *Hille* [55] filled their column with nylon powder which had been freed from monomers by precipitation. Development was carried out with 0.066 M phosphate buffer (at pH 6.8). The columns were heated to 60 °C to improve the partition efficiency. *Hörmann* and *von Portatius* [51,52] worked at room temperature with salt-free solvent mixtures consisting of dimethylformamide, glacial acetic acid, water, and ethanol. The R_F-values and elution mixture compositions are compiled in Table 6. Pronounced differences are evident between mono- and bis-dinitrophenyl-(DNP)-amino acids.

Table 6. R_F-Values of DNP-amino acids and DNP-peptides on polycaprolactam [52].

Dimethylformamide/glacial acetic acid/water/ethanol (5:10:30:20)

N(ε)-DNP-lysine	0.92	DNP-isoleucine	0.30
N(α)-DNP-arginine	0.86	DNP-glutamic acid	0.27
DNP-proline	0.57	DNP-phenylalanine	0.26
DNP-threonine	0.40	DNP-methionine	0.25
DNP-valine	0.33	DNP-aspartic acid	0.24
DNP-leucine	0.32	DNP-glycine	0.23
DNP-serine	0.32	DNP-tryptophan	0.15
DNP-alanine	0.31		

Dimethylformamide/glacial acetic acid/water/ethanol (8:15:25:20)

N(α),*N*(im)-bis-DNP-histidine	0.53
O,*N*-bis-DNP-tyrosine	0.48
N(α),*N*(δ)-bis-DNP-ornithine	0.21
N(α),*N*(ε)-bis-DNP-lysine	0.18

The latter are eluted with considerably more difficulty and require the use of more effective solvent mixtures than the mono-DNP derivatives. Unexpectedly, DNP-amino acids with zwitterionic properties, such as DNP-arginine or ε-DNP-lysine, are not retained by polycaprolactam (cf. the behavior of tyrosine, described above).

Information about the nature of the forces governing affinity between aromatic nitro compounds and polyamides was obtained from the sorption isotherms in several solvents [52]. The distribution of DNP-glycine between the solvent mixture dimethylformamide/glacial acetic acid/water/ethanol (5:10:30:20) and polycaprolactam follows a function, the graph of which approaches a straight line (Fig. 3, curve I). This again corresponds to

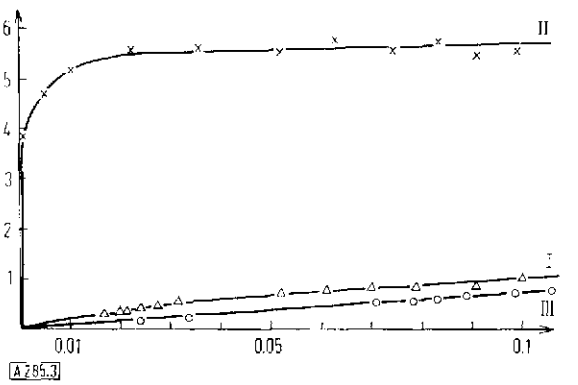


Fig. 3. Sorption isotherm of DNP-glycine on polycaprolactam and acetylated polycaprolactam [52].

I. Polycaprolactam; eluant: dimethylformamide/acetic acid/water/ethanol (5:10:30:20).
II. Polycaprolactam; eluant: ethanol.
III. Acetylated polycaprolactam; eluant: ethanol.
Ordinate: Concentration of DNP-glycine in the solid phase [mg/g].
Abscissa: Concentration of DNP-glycine in solution [mg/ml].

a distribution function which indicates a system endowed with relationships that are optimum for chromatographic separations. On the other hand, use of ethanol as solvent results in a sharply curved sorption isotherm, the rising branch of which points to a pronounced affinity of DNP-glycine towards polycaprolactam (Fig. 3, curve II). However, a saturation value is soon reached. The amount of DNP-glycine (23.4 μmoles/g of polycaprolactam) adsorbed up to the saturation point is equivalent to the number of free amino end-groups in the polymer. The assumption that the free amino groups represent the adsorption sites for the nitro compounds is confirmed by the sorption isotherm of DNP-glycine on acetylated polycaprolactam (Fig. 3). DNP-Glycine is taken up to only a small extent from alcoholic solution.

Acetylated polycaprolactam does not retain 1,3,5-trinitrobenzene. A few DNP-amino acids also travel considerably faster on acetylated polyamide than on free polyamide [56]. In contrast, it is found that the rate of travel of phenols is not diminished by acetylating the polycaprolactam; this is contrary to what would have been expected on the basis of the concept developed above of forces of affinity between phenolic hydroxyl groups and peptide bonds (Table 7).

The fact that aromatic nitro compounds tend to form molecular complexes with amines has been known for some time

[53] See also *H. Hörmann* and *H. Endres*, Z. Naturforsch. *10b*, 150 (1955); *B. Franck*, *H. Hörmann*, and *S. Scheibe*, Chem. Ber. *90*, 330 (1957).

[54] *F. Sanger*, Biochem. J. *39*, 507 (1945).

[55] *H. Steuerle* and *H. Hille*, Biochem. Z. *331*, 220 (1959).

[56] *H. v. Portatius*, Ph.D. thesis, Universität München, 1960.

Table 7. R_F-Values of nitro compounds and phenols on free and acetylated polycaprolactam

Compound	Eluant	R_F-Value on free polycaprolactam	R_F-Value on acetylated polycaprolactam
s-Trinitrobenzene	alcohol	0.00	0.81
O,N-Bis-DNP-tyrosine	dimethylformamide/glacial acetic acid/water/ethanol (5:10:30:20)	0.01	0.20
Picric acid		0.012	0.015 [*]
Styphnic acid		0.008 [**]	0.085 [**]
Phenol	water	0.20	0.20
1,3,5-Trihydroxybenzene	20 % acetone	0.20	0.22
2,4-Dihydroxybenzophenone	50 % methanol	0.20	0.22
4,4'-Dihydroxystilbene	50 % methanol	0.20	0.19
4,4'-Dihydroxybenzophenone	50 % methanol	0.17	0.22
Dihydropiceatannol	50 % methanol	0.11	0.10

[*] Strong tailing.
[**] Broad diffuse zone.

[57]. The association constants have been determined in some cases [58]. According to postulates of *Weiss* [59] and *Mulliken* [60], electron transfer from the amine to the nitro compounds takes place, analogous to an acid-base reaction. The formation of these complexes by charge transfer is indicated by a change in color and may be followed colorimetrically [61].

The retention of nitro compounds on polyamide corresponds, consequently, to the reaction of a Lewis acid with a base; for this reason, separation of nitro compounds on polycaprolactam columns may be conceived as an ion exchange process. Elution in sharp bands is thus only possible with solvents which have buffer properties [52].

Quinones

The sorption isotherms on acetylated and free polycaprolactam also gave an explanation for the peculiar behavior of quinones upon chromatography on polyamides [24]. Thus, *p*-benzoquinone travels rapidly with water or aqueous methanol. However, if the elution is interrupted for some time, it becomes impossible to elute the *p*-benzoquinone even with normally considerably more effective solvents, and the compound adheres irreversibly to the substratum. This process is combined with a change in color. The sorption isotherm

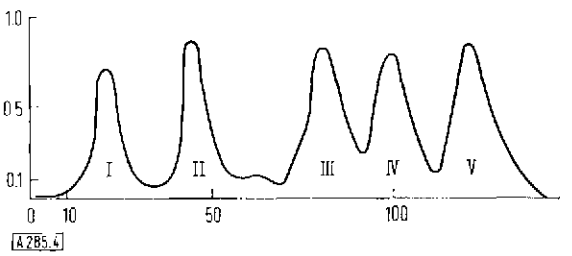


Fig. 4. Separation of *p*-benzoquinone (I), 2-hydroxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (II), 2,2'-dihydroxyazobenzene (III), 2,4'-dihydroxybenzophenone (IV), and 2,2'-dihydroxy-5,5'-dimethyldiphenylmethane (V) on a column filled with polyamide [24].
Solvent: methanol/water (1:1).
Ordinate: optical density at 546 mμ after the color reaction with Folin-Denis reagent.
Abscissa: ml of eluate.

of benzoquinone on polycaprolactam indicates saturation of the polyamide by reaction of one mole of benzoquinone with two moles of free amino groups. Clean separation of five quinonoid and phenolic substances on acetylated caprolactam has been achieved [24] (Fig. 4).

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[57] *P. Hepp*, Liebigs Ann. Chem. *215*, 345 (1882); *J. Meisenheimer, ibid, 323*, 219 (1902); *G. Briegleb* and *G. Angerer*, Angew. Chem. *64*, 685 (1952); Naturwissenschaften *40*, 107 (1953); *D. E. Laskowski* and *W. C. McCrone*, Analytic. *26*, 1497 (1954); *R. E. Miller* and *W. F. K. Wynne-Jones*, J. chem. Soc. (London) *1959*, 2375; Nature (London) *186*, 149 (1960).

[58] *B. Dale, R. Foster*, and *D. Ll. Hammick*, J. chem. Soc. (London) *1954*, 3986.

[59] *J. Weiss*, J. chem. Soc. (London) *1942*, 245.

[60] *R. S. Mulliken*, J. physic. Chem. *56*, 801 (1952); J. Amer. chem. Soc. *74*, 811 (1952).

[61] Titration of aromatic nitro compounds with amines: *H. Brockmann* and *E. Meyer*, Naturwissenschaften *40*, 242 (1953); Chem. Ber. *87*, 81 (1954); *J. S. Fritz, A. J. Maye*, and *M. J. Riehard*, Analytic. Chem. *29*, 1685 (1957).

COMMUNICATIONS

Cyanogen Di-N-oxide

By Prof. Dr. C. Grundmann

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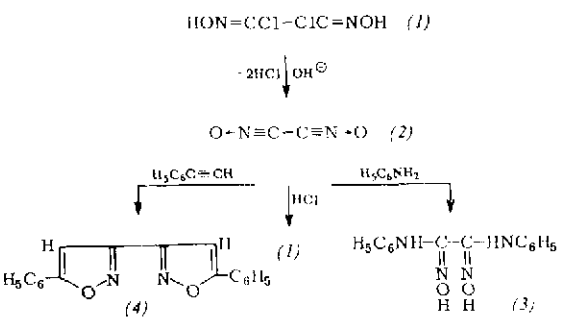
Solutions or suspensions of dichloroglyoxime *(1)* in water-immiscible, organic solvents react with weak aqueous alkalis to give solutions of the extremely reactive compound cyanogen di-*N*-oxide *(2)*, (oxalodinitrile di-*N*-oxide). The infrared spectrum of *(2)* has two main peaks at 2190 and 1235 cm^{-1}, that are characteristic for nitrile *N*-oxides [1]. The ultraviolet spectrum of a freshly prepared solution of *(2)* in n-hexane contains maxima at 312, 295, and 262 mμ; however, the spectrum changes rapidly because of polymerization of *(2)*. Cyanogen di-*N*-oxide is scarcely volatile with ether vapors, its solutions exhibit a very pungent odor, resembling a combination of bromine and formaldehyde. Inhalation of its vapors causes prolonged painful irritations of the upper respiratory tract. Attempts to isolate *(2)* from its solutions have so far only resulted in yellow to pink solid polymers which detonate on heating.



Dilute solutions of *(2)* are stable at 0 °C for several hours. Its identity was established by the following reactions [2]:

a) hydrogen chloride reforms dichloroglyoxime *(1)*, m.p. 204 °C (decomp.); b) *(2)* + aniline form oxaldianilidodioxime *(3)*, m.p. 218 °C (decomp.) [3]; c) phenylacetylene adds onto *(2)* to give 5,5′-diphenyl-3,3′-bisisoxazole *(4)*, m.p. 198 °C [4].

Reactions of type a) and b) have not yet been reported with aromatic nitrile *N*-oxides.

Cyanogen di-*N*-oxide readily undergoes 1,3-dipolar additions with unsaturated systems [5, 6] and adds on amines and acids. It is the first bifunctional nitrile *N*-oxide and reacts with other bifunctional addends, *e.g.* diolefines, diacetylenes, diamines, *etc.*, to give novel polymers.

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Publication withheld until now at the author's request

[1] *R. H. Wiley* and *B. J. Wakefield*, J. org. Chemistry *25*, 546 (1960).

[2] The formula shows only one of the possible mesomeric structures of *(2)*.

[3] *W. Steinkopf* and *B. Jürgens*, J. prakt. Chem. [2] *83*, 458 (1911).

[4] *A. Quilico*, *G. Gaudiano*, and *A. Ricca*, Gazz. chim. ital. *87*, 638 (1957).

[5] Cf. numerous publications of *A. Quilico* et al., in Gazz. chim. ital. since 1950; latest, *N. Barbulescu*, *P. Grünanger*, *M. R. Langella*, and *A. Quilico*, Tetrahedron Letters *1961*, 89.

[6] *R. Huisgen*, Proc. chem. Soc. (London) *1961*, 357; *R. Huisgen* and *W. Mack*, Tetrahedron Letters *1961*, 583; *R. Huisgen* and *E. Anneser*, ibid. *1961*, 587; *R. Huisgen*, *W. Mack*, and *E. Anneser*, Angew. Chem. *73*, 656 (1961).

Partially Asymmetric Synthesis of 2-Phenylcyclopropanecarboxylic Acid

By Dipl.-Chem. I. Tömösközi

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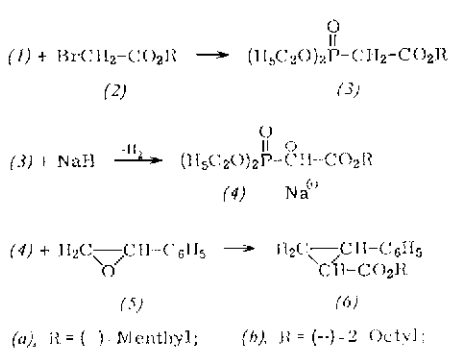
Treatment of epoxides with phosphorylenes, phosphonate carbanions, or phosphine oxide carbanions yields derivatives of *trans*-cyclopropane, together with phosphine oxides, phosphates, or phosphinates, respectively. According to *Wittig* [1], the mechanism resembles that of the reaction between diethyl (−)-menthoxycarbonylmethylphosphonate *(3a)* and 4-alkylcyclohexanone [2]. Phosphonate carbanions are most suitable for the preparation of cyclopropane derivatives. Alkylphosphonic esters containing an electron-attracting group (*e.g.* COOR) in the α-position are readily metallated with alkoxides or sodium hydride. Compound *(3a)* and diethyl (−)-2-octoxycarbonylmethylphosphonate *(3b)* were prepared in good yield from triethyl phosphite *(1)* and the bromoacetic esters *(2a)* or *(2b)*; their hydrolysis with acid yielded the same phosphonoacetic acid [*(3c)*, with H instead of C_2H_5].



(a), R = (−)-Menthyl; *(b)*, R = (−)-2-Octyl; *(c)*, R = H.

With NaH in 1,2-dimethoxyethane, *(3a)* and *(3b)* yield the carbanions *(4a)* or *(4b)*. On treatment with styrene oxide *(5)* for 4 hours at 70 °C, these afford the cyclopropane derivatives *(6a)* or *(6b)* in 40–42 % yield. Alkaline hydrolysis produces (+)-*(6c)* in both cases.

Reaction	*(6c)* $[\alpha]_D$	Optical Purity [3] [%]
(4a) + *(5)*	16.5°	6.1
	17.5°	6.5
(4b) + *(5)*	12.0°	4.45
	13.2°	5.07

The reaction mixtures containing *(6a)* and *(6b)* were immediately hydrolysed. The acids *(6c)* showed almost the same $[\alpha]_D$ values as those obtained from the purified esters. Authentic (−)-menthyl or (−)-2-octyl (+)-*trans*-2-phenylcyclopropanecarboxylate is readily available by acylation of (−)-menthol or (−)-2-octanol with (±)-*trans*-2-phenylcyclopropionyl chloride [4] in boiling $CHCl_3$. Alkaline hydrolysis gave optically inactive *(6c)*. Hence, a partial hydrolysis, that might account for the optical activity, is therefore out of the question (compare also [3]).

Received, January 28th, 1963 [Z 442/268/IE]

[1] *G. Wittig*, *W. Böll*, and *K. H. Krück*, Chem. Ber. *95*, 2514 (1962).

[2] *I. Tömösközi* and *G. Janzso*, Chem. and Ind. *1961*, 2085.

[3] *I. Tömösközi*, J. org. Chemistry, in the press.

[4] *R. S. Ratney* and *J. English, Jr.*, J. org. Chemstry *25*, 2213 (1960).

Electrofluorination of Gases

By Dr. P. Sartori

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The known processes [1] for electrofluorination, *i.e.* for electrolysis in liquid, anhydrous HF at about or below 0 °C can only be applied to HF-resistant, relatively non-volatile substances which can be dissolved, suspended, or emulsified in HF. Elevated pressure is only applicable to a limited extent. We have found that gases that are insoluble in HF can be electrofluorinated at atmospheric pressure if they are forced through the electrolyte from below in as finely divided a form as possible during the electrolysis (0.4–0.6 A/dm²; 5–7 V) so that they pass between the electrodes, which are suspended next to one another at a distance of 2–5 mm (total area *ca.* 3500 cm²); no separating diaphragms are used. About 5 % w/w KF or NaF are added to the anhydrous HF to increase its conductivity. The current yields are approximately of the same order as those in technical electrofluorinations [2].

Propane gives a total current yield of 30–33 %, the product comprising mainly C_3F_8, CF_3–CHF–CF_3, and CF_3–CF_2–CHF_2, as well as a little CF_4 and $C_3F_6H_2$. Ethane leads to a 16 % current yield of C_2F_6 (26.2 % reaction yield based on ethane), 3.5 % C_2F_5H (10.3 %), 4.2 % $C_2F_4H_2$ (10 %), and 0.3 % CF_4. Methane gives an 8.1 % current yield of CF_4 and 11 % CF_3H, together with a little CF_2H_2 and CFH_3. (The current yield is calculated from the quantity of current used according to Faraday's law; c–H + F_2 → c–F + HF; c = 1/4 C).

The reaction products and excess hydrocarbon can be condensed out with liquid air without any danger, provided all the OF_2, which is formed from moisture present in the electrolyte, is removed. This is achieved by thorough washing, first with semisaturated Na_2SO_3 solution containing some KI and then with 20 % caustic potash. If this precaution is not taken, violent explosions can occur after OF_2 has accumulated.

When H_2S is electrofluorinated in moist electrolyte, a poor yield of SO_2F_2, SOF_2, and SF_4 is obtained as a difficultly separable mixtnre. In dry electrolyte, on the other hand, SF_6 is obtained in 40 to 42 % current yield (calculated according to:

$H_2S + 4F_2 \rightarrow SF_6 + 2HF$). Sulfur oxyfluorides are then present only in traces. SF_6 is completely pure after a single washing with 10 % caustic potash. On electrofluorination of N_2O, products are formed which explode after condensing in liquid air.

Most of the fluorination products mentioned are known, but hitherto they could only be prepared by using elementary fluorine.

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Publication withheld until now at the author's request

[1] U.S. Pat. 2519983 (Aug. 22nd, 1950), Minnesota Mining & Manufacturing Co.; inventor: *J. H. Simons*; U.S. Pat. 2806817 (Sept. 17th, 1957), General Electric Co.; inventor: *J. K. Wolfe*.

[2] *J. C. Tatlow, M. Stacey*, and *A. G. Sharpe:* Advances in Fluorine Chemistry. Butterworth Scientific Publications, London 1960, Vol. 1, p. 129 et seq.; *Houben-Weyl:* Methoden der organischen Chemie. Georg Thieme Verlag, Stuttgart 1962, Vol. V/3, pp. 38-42.

Silicon Tetrakisdiethylphosphide

By Prof. Dr. G. Fritz [1] and Dr. G. Poppenburg

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der Universität Münster (Germany)

In continuation of our investigations on derivatives of H_3SiPH_2 [2], we have prepared $Si[P(C_2H_5)_2]_4$ *(1)*, b.p. ca. 160 °C/1 mm, by treating $SiCl_4$ with $LiP(C_2H_5)_2$ in a ratio of 1:4. In addition to *(1)*, considerable quantities of $[(C_2H_5)_2P]_2$ are formed. Compound *(1)* is decomposed by alkali as follows:

$$Si[P(C_2H_5)_2]_4 + 4\,H_2O \xrightarrow{NaOH} \{Si(OH)_4\} + 4\,(C_2H_5)_2PH$$

The reaction proceeds quantitatively on warming. The $HP(C_2H_5)_2$ *(2)* formed is transformed by $HgCl_2$ solution into the sparingly soluble compound $(C_2H_5)_2PHgCl$. This can be used to estimate *(2)* quantitatively by subsequent iodometric titration. Compound *(1)* ignites in air and is extremely sensitive to moisture.

Received, February 10th, 1963 [Z 456/287 IE]

[1] New adress: Institut für Anorganische und Analytische Chemie der Universität Gießen (Germany).

[2] *G. Fritz*, Z. anorg. allg. Chem. *280*, 332 (1955); *G. Fritz* and *G. Poppenburg*, Angew. Chem. *72*, 208 (1960); *G. Fritz, G. Poppenburg*, and *M. G. Rocholl*, Naturwissenschaften *49*, 255 (1962); *G. Fritz* and *G. Poppenburg*, ibid. *49*, 449 (1962).

Explosion during the Destruction of Dimethyl Sulfate with Ammonia

By Dr. H. Lindlar

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Excess dimethyl sulfate left over after methylations must be destroyed because of its poisonous nature. Ammonia is widely recommended for this purpose in the literature. Through an experimental error about 1.5 l of dimethyl sulfate were brought into contact with 1–2 l of concentrated aqueous ammonia. After about 10 seconds, an extremely violent reaction occurred which shattered the flask. The fragments injured a workman, and several windows were broken. Fortunately, the accident occurred in the open and caused no extensive damage; no symptoms of poisoning through inhalation of dimethyl sulfate were observed.

Experiments with smaller quantities showed that pure dimethyl sulfate and concentrated aqueous ammonia react extremely violently with one another [1].

When destroying dimethyl sulfate with ammonia, the latter should therefore only be added diluted and in small quantities.

Received, February 12th, 1963 [Z 447/277 IE]

[1] Cf. *P. Claesson* and *C. F. Lundvall*, Ber. dtsch. chem. Ges. *13*, 1700 (1880).

Application of the Becquerel Effect to the Investigation of Photochemical Reactions

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der Universität Tübingen (Germany)

We are investigating the Becquerel effect displayed by dissolved organic substances [1]. If two identical electrodes are introduced into a solution of a suitable organic compound and one electrode is illuminated, a potential difference, which becomes stable after a few minutes, is established between them. The potential difference disappears again after a time if the light source is switched off.

Over 100 systems were examined; aromatic and aliphatic oxo and dioxo compounds, aromatic nitro compounds, aliphatic halogeno compounds, and nitrous esters, as well as polymerizable unsaturated compounds in polar solvents such as alcohols, dimethyl sulfoxide, or tetramethylene sulfone. The photochemical potentials and currents were measured as functions of time in relation to wave length and intensity [2]. A correlation between ability to fluoresce and Becquerel activity, as reported in the older literature, could not be established. Only those systems show this effect which react photochemically under our experimental conditions and which undergo reactions where radical mechanisms are either established or probable. Systems in which *cis* → *trans* rearrangement or isomerization takes place are, as far as has been investigated, inactive.

The results of our measurements lead to the conclusion that radicals occur as intermediates and exchange electrons with the illuminated electrode, which thus accumulates a charge. All our potential *vs.* time curves can be reduced to a few types. Parallels between curves and type of reaction are indicated. The growth and decay curves can frequently be interpreted as being formed by superposition of two simple curves with equal or opposite sign. The conclusion that can be drawn from this is that different radical intermediates occur. As expected, the purity of the materials used as well as the presence of oxygen and other radical acceptors influence the shapes of the curves.

As our work stands at present, the Becquerel effect can be used to detect photochemical reactions involving radical mechanisms and to determine the effective spectral ranges for them, in particular their limits in the long-wave region. In favorable circumstances, it is possible to identify the mechanisms by their different spectral regions.

Received, February 25th, 1963 [Z 455/285 IE]

[1] *E. Becquerel*, C. R. hebd. Séances Acad. Sci. *9*, 145 (1839). Most recent review: *A. W. Copeland, O. D. Black*, and *A. B. Garrett*, Chem. Reviews *31*, 177 (1942).

[2] For experimental details, see *U. Sproesser*, Diploma thesis, Universität Tübingen, 1962.

Intramolecular Coupling of Diazotized N-(2-Aminophenyl)pyrrole to form Pyrrolo[1,2-c][1,2,4]benzotriazine

By Dr. H. Gross and Dipl.-Chem. J. Gloede

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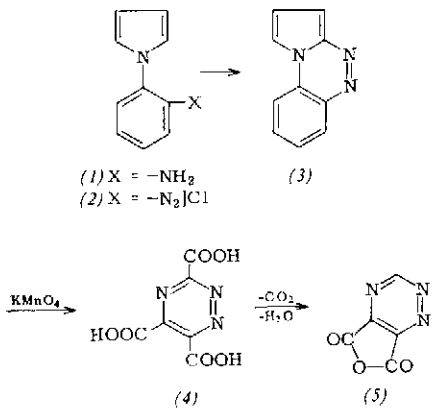
On diazotizing *N*-(2-aminophenyl)pyrrole *(1)* [1] in aqueous acidic medium, we immediately obtained not the expected diazonium salt *(2)* but a yellow, crystalline compound of m.p. 243–244 °C in over 90 % yield. Analysis and molecular-weight determination indicate that this compound has the formula $C_{10}H_7N_3$.

The assumption that the hitherto unknown compound pyrrolo[1,2-*c*] [1,2,4]benzotriazine *(3)* is formed from *(2)* in

an intramolecular coupling reaction was confirmed by oxidative degradation: on boiling *(3)* with aqueous potassium permanganate, 1,2,4-triazine-3,5,6-tricarboxylic acid



(4) was obtained, and from it 1,2,4-triazine-5,6-dicarboxylic anhydride *(5)* m.p. 175–183 °C ([2] gives 176–184 °C).

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[1] *H. Gross*, Chem. Ber. *95*, 2270 (1962).

[2] *R. Rätz* and *H. Schroeder*, J. org. Chemistry *23*, 1931 (1958).

Tetrasilapiperazine – a New SiN Ring System [1]

By Prof. Dr. U. Wannagat and Dipl.-Ing. O. Brandstätter

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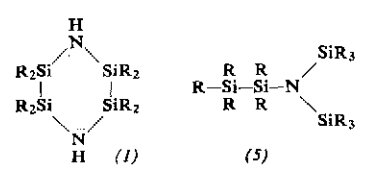
Four-, six-, and eight-membered silicon-nitrogen rings with alternating Si–N units have been known for quite a long time [2–4]. After the preparation of an Si_2N_4 ring in $(-R_2Si-NH-NH-)_2$ and its derivatives [5,6], we have now also found an Si_4N_2 ring ("tetrasilapiperazine") in 2,3,5,6-octamethyl-1,4-diaza-2,3,5,6-tetrasilacyclohexane *(1)*, m.p. +1 °C, b.p. 61 °C/2 mm, $n_D^{20} = 1.4760$, $d_4^{20} = 0.8458$, a compound we obtained by treating 1,2-dichlorotetramethyldisilane with gaseous ammonia in a solution of petroleum ether (R=CH_3 throughout):

$$2\ ClR_2Si-SiR_2Cl + 6\ NH_3 \rightarrow 4\ NH_4Cl + (-R_2Si-SiR_2-NH-)_2$$

Ammonolysis of pentamethylchlorodisilane *(2)* leads smoothly to bis(pentamethyldisilanyl)amine $(R_3SiSiR_2)_2NH$ *(3)*, b.p. 102–103 °C/13 mm, $n_D^{20} = 1.4609$, $d_4^{20} = 0.8154$. Compound *(3)* can be transformed by $NaNH_2$ in benzene with evolution of NH_3 into the *N*-metallated derivative $NaN(Si_2R_5)_2$, m.p. 58–62 °C, which is highly sensitive to moisture and air. Compound *(2)*, on the other hand, reacts only sluggishly and non-uniformly with sodium bis(trimethylsilyl)amide *(4)*. We managed to isolate almost pure (>90 %) *N*-pentamethyldisilanyl-*N*,*N*-bis(trimethylsilyl)amine *(5)*, (b.p. 90–93 °C/14 mm, m.p. < −70 °C, $n_D^{20} = 1.442$, $d_4^{20} = 0.822$) from the reaction products. Analogous reaction of *(4)* with hexachlorodisilane, too, has so far only proceeded to the stage of an *N*-pentachlorodisilanyl-*N*,*N*-bis(trimethylsilyl)amine, b.p. 78–80 °C/1mm, which also contained 20 % 1,2-di(bis-trimethylsilylamino)tetrachlorodisilane.



The infrared spectra of *(1)* and *(3)* display characteristic, very strong bands of ν_{as} SiNSi at 925 and 920 cm^{-1}, and also of δ_{NH} at 1141 and 1172 cm^{-1}. The NH-band in bis-silylamines is normally situated at 1180 cm^{-1} but appears in a distinctly weakened form in the ring of *(1)*. It is thus comparable to the δ_{NH}-band in the planar $(-R_2Si-NH-)_3$ ring (1159 cm^{-1}).

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[1] Communication No. 29 on SiN-compounds. Communication No. 22: Angew. Chem. internat. Edit. *2*, 46 (1963); Comm. Nos. 23 and 24: Chem. Ber.; Nos. 25–28: Z. anorg. allg. Chem. (in the press).

[2] *H. Ernst*, Ph. D. thesis, Technische Hochschule Aachen, 1958.

[3] *W. Fink*, Angew. Chem. *73*, 736 (1961).

[4] *S. D. Brewer* and *C. P. Haber*, J. Amer. chem. Soc. *70*, 3888 (1948).

[5] *U. Wannagat* and *H. Niederprüm*, Angew. Chem. *70*, 745 (1958); Z. anorg. allg. Chem. *311*, 270 (1961).

[6] *M. V. George*, *D. Wittenberg*, and *H. Gilman*, J. Amer. chem. Soc. *81*, 361 (1959).

Polyhydroxyamines via Diene Syntheses with Nitroso Compounds

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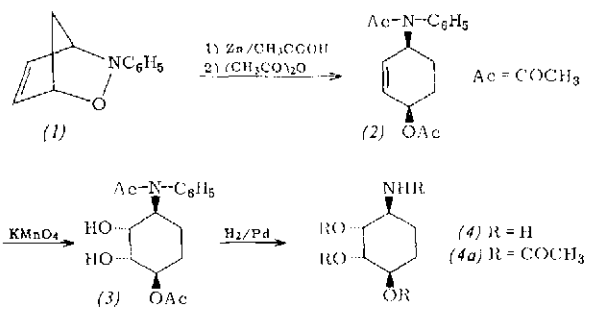
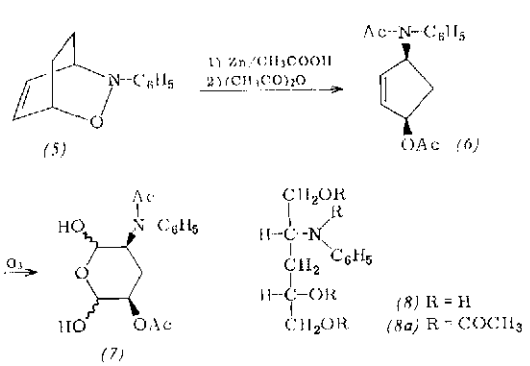
We have shown [1] that 1-amino-2-butene-4-ol derivatives can be prepared stereospecifically by way of diene synthesis with –N=O dienophiles. In the products, the NH_2- and the OH-groups are *erythro* to one another, and the substituents on the carbon-carbon double bond are in *cis*-relationship. Starting from such compounds, polyhydroxyamino compounds of known stereochemistry can be obtained; these are of interest, for example, as aminosugar or inosamine derivatives (see *e.g.* [2]). Here we have investigated the following possibilities:

1. Cyclohexadiene derivatives give inosamine derivatives. We have prepared compounds *(1)* through *(4a)* as models.



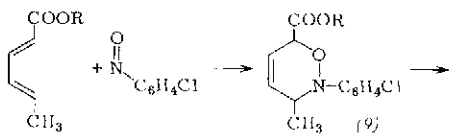
Nitrosobenzene + cyclohexadiene → 3-phenyl-[2-oxa-3-aza-bicyclo[2,2,2]-5-octene (m.p. 65 66 °C) → *cis*-1-(*N*-acetyl-anilino)-4-acetoxy-2-cyclohexene (m.p. 56–57 °C) → 1-(*N*-acetylanilino)-2-*trans*-3-*trans*-dihydroxy-4-*cis*-acetoxycyclohexane *(3)* (tetraacetyl derivative of *(3)* has m.p. 130–131 °C; the stereochemistry is based on the acetanilido group) → a dideoxyinosamine, 1-aminocyclohexane-2-*trans*-3-*trans*-4-*cis*-triol *(4)*; the tetraacetate *(4a)* has m.p. 93–95 °C.



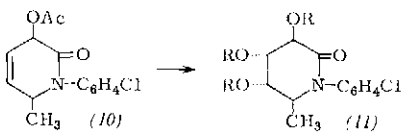
2. The use of cyclic dienes and ring cleavage at the site of the double bond afford aminohydroxy-ω,ω'-dialdehydes, which can be reduced to aminopolyols.

The adduct *(5)* obtained from cyclopentadiene and nitrosobenzene (m.p. of *(5)* = 32–34 °C) can be reduced to *cis*-1-(*N*-acetylanilino)-4-acetoxy-2-cyclopentene (m.p. 102–103 °C), which on ozonisation, or oxidation to the glycol and cleavage with periodate yields the *erythro*-2-(*N*-acetylanilino)-4-acetoxyglutardialdehyde, which exists as a cyclic semiacetal of the monohydrate *(7)*. On reduction with $NaBH_4$, *(7)* gives the *N*-phenyl-2,3-dideoxy-2-aminoerythritol *(8)*, which yields a tetraacetyl derivative *(8a)*.

3. Hexose derivatives are accessible by the use of appropriate dienes, *e.g.* sorbic acid derivatives [2]. We have carried out the following reactions:



(9)



(10) *(11)*

2-(*p*-Chlorophenyl)-3-methyl-6-ethoxycarbonyl-3,6-dihydro-1,2-oxazine *(9)*, m.p. 63 °C; → *N*-(*p*-chlorophenyl)-2-methyl-5-acetoxy-1-azahex-3-en-6-one *(10)*, m.p. 120 °C; → *N*-(*p*-chlorophenyl)-5,6-didesoxy-5-amino-DL-allonolactam *(11)* m.p. 166 °C.

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[1] *G. Kresze* and *G. Schulz*, Tetrahedron *12*, 7 (1961).

[2] *B. Belleau* and *Yum-Kin Au-Young*, J. Amer. chem. Soc. *85*, 69 (1963).

Silyl-substituted Aluminum-triamide [1]

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The well-known compound sodium bis(trimethylsilyl)amide [2] proved to be readily accessible by the following reaction (a)

$$NaH + HN[Si(CH_3)_3]_2 \rightarrow NaN[Si(CH_3)_3]_2 + H_2 \quad (a)$$

Extension of this reaction to lithium aluminum hydride results in reaction according to equation (b)

$$LiAlH_4 + 4\ HN[Si(CH_3)_3]_2 \rightarrow$$

$$LiN[Si(CH_3)_3]_2 + Al\{N[Si(CH_3)_3]_2\}_3 + 4\ H_2 \quad (b)$$

The lithium compound is readily removed by crystallisation, leaving aluminum hexakis(trimethylsilyl)triamide *(1)* as colorless crystalline needles which sublime readily *in vacuo* and which are soluble in non-polar organic solvents, m.p. 500 °C with slow decomposition.

In contrast to silyl-substituted aluminum trihydroxide $Al[OSi(CH_3)_3]_3$ *(2)* [3,4], *(1)* is monomeric according to cryoscopic molecular-weight determinations and shows no tendency to add on further atoms to the aluminum beyond the coordination number 3. No complex formation occurs with lithium bis(trimethylsilyl)amide, which is also formed according to equation (b), sodium trimethylsiloxide, or ether [2,5]. In contrast to *(2)* [3], the proton magnetic resonance spectrum of the highly symmetrical compound *(1)* shows only one distinct signal (chemical shift in CCl_4 compared with $Si(CH_3)_4$ as internal standard: 0.244 ppm) – a remarkable observation for a compound containing 54 hydrogen atoms per molecule – and therefore precludes any bridged structures. The central aluminum atom is inaccessible because the groups surround it spherically. In spite of this, water splits the aluminum-nitrogen bond exothermically before affecting the silicon-nitrogen link.

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[1] Communication No. 30 on silicon-nitrogen compounds.

[2] *U. Wannagat* and *H. Niederprüm*, Chem. Ber. *94*, 1540 (1961).

[3] *H. Schmidbaur* and *Max Schmidt*, Angew. Chem. internat. Edit. *1*, 328 (1962).

[4] *H. Schmidbaur* and *Max Schmidt*, Angew. Chem. internat. Edit. *1*, 549 (1962).

[5] *U. Wannagat* and *H. Kuckertz*, Angew. Chem. internat. Edit. 2, 47 (1963).

Oxo-osmates(VII)

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Recently, *Ward* [1] reported the preparation of compounds of general formula $Me^{II}_2Me^{I}OsO_6$, where Me^{II} = Ba, Sr, or Ca and Me^{I} = Li or Na. *Bartlett* [2] described the compound $OsOF_5$. Both authors claim to have obtained compounds of heptavalent osmium probably for the first time. We had in fact prepared two alkali osmates(VII), *viz.* Li_5OsO_6 and Na_5OsO_6, in 1958 [3] by causing metallic osmium to react with alkali oxides in a stream of oxygen at 550 °C. They are isotypic with the corresponding oxorhenates(VII) [3,4] and oxoiodates(VII). Li_5OsO_6 was shown to be hexagonal.

In the course of investigations completed in 1959 [5], three pure osmates(VII) were prepared, *viz.* Na_3OsO_5, K_3OsO_5, and $Ba_5(OsO_6)_2$. The compound Na_3OsO_5 is isotypic with Na_3ReO_5 and is prepared using Na_2O analogous to the preparation of Na_5OsO_6. K_3OsO_5 is best prepared from K_2OsO_4 and KO_2 in a stream of nitrogen at 500 °C; it is isotypic with K_3ReO_5 and K_3IO_5 [3, 4]. Hexaoxo salts of the type K_5MeO_6 (Me = Os, Re, or I) could not be obtained. Oxidation of metallic Os in the presence of BaO is too slow for convenient preparation of $Ba_5(OsO_6)_2$. However, on causing $BaOsO_4 \cdot 4H_2O$ to react with BaO (Ba : Os = 2.5 : 1) in a stream of nitrogen at 700 °C, the product is an equimolar mixture of Ba_2OsO_5 and Ba_3OsO_6 [6], which can be oxidized by O_2 at 500 °C to give $Ba_5(OsO_6)_2$. Barium hexaoxo-osmate(VII) is isotypic with the corresponding oxorhenate(VII) and oxoiodate(VII) [4].

All the oxo-osmates(VII) described above are black; in water they disproportionate to give OsO_4 and osmates(VI). They are reduced by methanol and ethanol to the Os(VI) state. At 800 °C in a stream of nitrogen, Na_5OsO_6 or $Ba_5(OsO_6)_2$ disproportionate to give OsO_4 and Na_4OsO_5 or Ba_3OsO_6, respectively; under the same conditions, after addition of 0.5 mole of Li_2O, Li_5OsO_6 can be degraded to Li_6OsO_6.

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[1] *R. Ward* et al., Inorg. Chem. *1*, 257 (1962).

[2] *N. Bartlett* et al., Proc. chem. Soc. (London) *1962*, 277; Nachr. Chem. Techn. *10*, 313 (1962).

[3] *R. Scholder*, Angew. Chem. *70*, 591 (1958).

[4] *K. L. Huppert*, Ph.D. Thesis, Technische Hochschule Karlsruhe, 1959.

[5] *G. Schatz*, Ph.D. Thesis, Technische Hochschule Karlsruhe, 1959.

[6] *R. Scholder* and *G. H. Stephan*, unpublished results; see *G. H. Stephan*, Ph.D. Thesis, Technische Hochschule Karlsruhe, 1960.

Preparation and Properties of Oxorhenates(VI) and Oxorhenates(VII)

By Prof. Dr. R. Scholder [1], Dr. K. L. Huppert [2], and Dr. P. P. Pfeiffer [3]

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Alkali and alkaline-earth oxorhenates(VII) and oxorhenates(VI) were prepared by thermal reaction of appropriate mixtures in the solid phase. They were unequivocally differentiated by quantitative analysis, X-ray analyses (as far as possible by determination of the lattice parameters), and in some cases by determination of their solubilities in absolute methanol.

In addition to tetraoxorhenates(VII) of the type $Me^{I}ReO_4$ and $Me^{II}(ReO_4)_2$ (Me = metal cation), penta- and hexaoxorhenates containing Re^{VII} were prepared by thermal reaction of the corresponding tetraoxorhenate(VII) with oxides or carbonates of Li, Na, Ba, Sr, or Ca; in order to obtain K_3ReO_5, KOH was used as the basic component. Pentaoxorhenates of the type $Me^{I}_3ReO_5$ or $M^{II}_3(ReO_5)_2$ were obtained with Na and K as Me^{I} and Ba and Sr as Me^{II}. Na_3ReO_5 and K_3ReO_5 are isotypes of the corresponding osmates(VII) [4]; furthermore, the compound K_3IO_5, which is isotypic with K_3ReO_5, was prepared for the first time. There are two modifications of $Ba_3(ReO_5)_2$. Hexaoxorhenates of the type $Me^{I}_5ReO_6$ or $Me^{II}_5(ReO_6)_2$ (Me^{I} = Li, Na; Me^{II} = Ba, Sr, Ca) are isotypic with the corresponding osmates(VII) [4] and iodates(VII). Li_5ReO_6 was assigned to the hexagonal system (lattice constants: $a_0 = 5.05_3$ Å, $c_0 = 14.21$ Å, $c/a = 2.81$). The yellow to orange color of oxorhenates(VII) with higher oxygen co-ordination is noteworthy, in contrast to the tetraoxorhenates, which are colorless; they are split immediately by water into tetraoxorhenates(VII) and free base. Rhenates containing Re^{VI} are obtained by interaction of oxorhenates(VII), metallic Re, and the appropriate quantity of a basic oxide. In the system Li_2O-ReO_3, the compounds Li_4ReO_5 and Li_6ReO_6 both exist in two modifications. The low-temperature form of Li_4ReO_5 has the Lang structure [5] and probably has the formula $Li_2[Re_{0.6}Li_{0.4}]O_3$, while α-$Li_4ReO_5$ is isotypic with Li_4WO_5 [6] and Li_4TeO_5 [7]. The fact that β-Li_6ReO_6 and Li_5ReO_6 are clearly isotypes is worthy of note (lattice constants of β-Li_6ReO_6: $a_0 = 5.03$ Å, $c_0 = 14.12$ Å, $c/a = 2.81$). The compound Li_4MgReO_6 was also prepared for the first time and has the same type of structure. Li_6OsO_6 [8] crystallizes in a similar lattice. α-Li_6ReO_6 is isotypic with Li_6WO_6 [6]; it cannot be indexed from its powder diagram.

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[1] *R. Scholder*, Angew. Chem. *70*, 583 (1958).

[2] *K. L. Huppert*, Ph.D. Thesis, Technische Hochschule Karlsruhe, 1959.

[3] *P. P. Pfeiffer*, Ph.D. Thesis, Technische Hochschule Karlsruhe, 1963.

[4] *G. Schatz*, Ph.D. Thesis, Technische Hochschule Karlsruhe, 1959.

[5] *G. Lang*, Z. anorg. allg. Chem. *276*, 77 (1954).

[6] *R. Scholder* and *L. H. Brixner*, unpublished results.

[7] *V. Schneider*, Ph.D. Thesis, Technische Hochschule Karlsruhe, 1959.

[8] *G. H. Stephan*, Ph.D. Thesis, Technische Hochschule Karlsruhe, 1960.

Ternary and Quaternary Compounds of Tri- to Hexavalent Rhenium

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The ease with which the valence of rhenium can be altered facilitates thermal symproportionation and disproportionation reactions leading to new oxorhenates containing trivalent to hexavalent Re.

In the ternary system Me–Re–O, there are compounds with the ordered perovskite structure and the composition Me_3ReO_6 (Me = Ba, Sr, Ca) [3]. However, of these only Ba_3ReO_6, which was obtained in two tetragonal modifications, could he indexed from a powder diagram. Of the compounds of the type $Me'Me''ReO_6$, all the combinations with Me' = Ba, Sr, or Ca and Me'' = Ba, Sr, Ca, or Mg were prepared (partly in agreement with the results of *Ward* [4]); all the compounds possess the ordered perovskite structure. Furthermore, a rhombohedral phase $Ba_3ReO_6 \cdot 0.3BaO$ was obtained pure. Compounds of the type $Me_5Re_2O_{11}$ (Me = Sr or Ca) also possess the perovskite structure. The new compounds Ba_2ReO_5 (isotypic with Ba_2XO_5, X = Te, Mo, W, or Os) [5] and Sr_2ReO_5 [6] (isotypic with Sr_2WO_5) were also prepared. Compounds of the type $Me_3Re_2O_9$ (Me = Ba, Sr, or Ca) show structural relationships with $Me^{II}_3(PO_4)_2$ [corresponding formula $Me_3(ReO_{4.5})_2$].

Of the ternary compounds containing Re^{V}, only Li_3ReO_4 and $Ca_2Re_2O_7$ could be prepared. The low-temperature form of Li_3ReO_4 has the Lang structure [7] (corresponding formula: $Li_2[Re_{0.75}Li_{0.25}]O_3$); the high-temperature form is cubic, like Li_3OsO_4 [8] and Li_3TaO_4.

Additional oxorhenates(V) were obtained from quaternary systems Me^1-Me^2-Re-O in which a second basic component promotes the stabilization of the Re^{V} in energetically favorable lattice types. In this way, $Li_2[Re_{0.67}Mg_{0.33}]O_3$, which possesses the Lang structure, was obtained. Furthermore, compounds of the type $Ba_2Me^{III}ReO_6$ (Me^{III} = a rare-earth (RE) metal, Sc, Y, or In), which possess the ordered perovskite structure, were prepared. Precise determination of the lattice constants in the isostructural series $Ba_2(RE)ReO_6$ gave no crystallographic effect with Gd. The lattice constants of the compounds containing Ce, Pr, or Tb are lower than the values expected, indicating partial charge transfer in accordance with:

$$Ba_2(RE^{III})Re^{V}O_6 \leftrightarrow Ba_2(RE^{IV})Re^{IV}O_6.$$

Reactions in quaternary systems which ought to produce oxorhenates (IV), invariably give compounds containing rhenium of higher and lower valence and, in limiting cases, even some elemental rhenium. Na_2ReO_3 disproportionates partially on heating for a long period to form Na_3ReO_5 and elemental Re. Oxorhenates(IV) of Ca could not be obtained [9].

Oxorhenates(III): on treating Li_2O with ReO_2 under varying conditions, disproportionation of the Re^{IV} occurs and $LiReO_2$, among other products, is formed. It can be purified and shown to be cubic. It is isotypic with another new compound $LiWO_2$.

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[1] *R. Scholder*, Angew. Chem. internat. Edit. *1*, 220 (1962).

[2] *P. P. Pfeiffer*, Ph.D. thesis, Technische Hochschule Karlsruhe, 1963.

[3] *K. L. Huppert*, Ph.D. thesis, Technische Hochschule Karlsruhe, 1959.

[4] *R. Ward* et al., Inorg. Chem. *1*, 245 (1962).

[5] *R. Scholder*, Angew. Chem. *70*, 583 (1958).

[6] *R. Scholder* and *L. H. Brixner*, unpublished results.

[7] *A. Lang*, Z. anorg. allg. Chem. *276*, 77 (1954).

[8] H. Gläser, Ph.D. thesis, Technische Hochschule Karlsruhe, 1961.

[9] Contrast *A. Deschanvres*, Ann. Chim. *4*, 1217 (1959).

Hexabenzooctalene from Tribenzotropone

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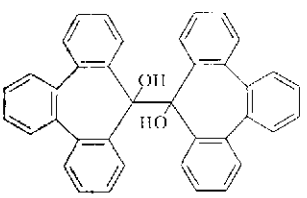
Tribenzotropone *(1)* is readily obtained from the Diels-Alder adduct formed from furan and 4,5-dehydro-2,3:6,7-dibenzotropone [1] by catalytic hydrogenation followed by elimination of water. Reduction of *(1)* with magnesium/magnesium

iodide in ether/benzene led to the pinacol *(2)*, m.p. 220–221 °C; 30–35 % yield, which readily undergoes pinacol rearrangement with glacial acetic acid/sulfuric acid or with phosphorus pentoxide in xylene to give the spiroketone *(3)*, m.p. 252 to 254 °C; 75 %. The action of acids on the carbinol *(4)*, m.p. 247–248 °C, prepared from *(3)* and $LiAlH_4$, yields a colorless hydrocarbon $C_{38}H_{24}$ *(5)*, m.p. 289–290 °C, in 75 % yield, which, according to spectral analyses, contains only aromatic protons and only *o*-disubstituted benzene rings and which is not identical with hexabenzoheptafulvalene (m.p. 401–403 °C). The latter can be prepared from 1,1-dichloro-2,3:4,5:6,7-tribenzotropilidene and phenyl-lithium [2], and also with copper powder in benzene. Hence *(5)* is a hexabenzooctalene, as is also indicated by its ultraviolet spectrum (λ_{max} = 233 mμ; log ε = 4.97 in dioxan). The similarity of the ultraviolet spectra of *(5)* and tetraphenylene or dibenzocyclooctatetraene indicates that hexabenzooctalene is not planar and that two stereoisomers have to be considered. It appears that the ring expansion from *(1)* to *(5)*, corresponding to that already carried out successfully with smaller rings [3], also goes smoothly from the seven- to the eight-membered ring.



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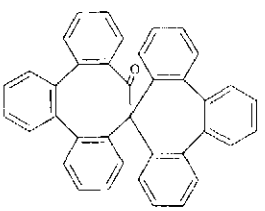

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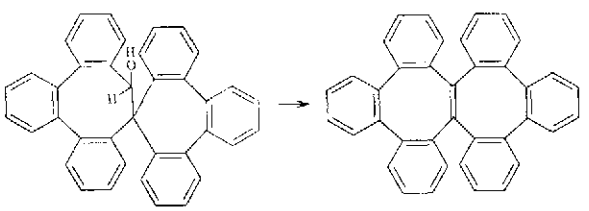

(4) *(5)*

Received, March 20th, 1963 [Z 471/298 IE]

[1] *W. Tochtermann*, Angew. Chem. internat. Edit. *1*, 403 (1962).

[2] *G. Wittig* and *H. Witt*, Ber. dtsch. chem. Ges. *74* 1474 (1941) prepared tetraphenylethylene from diphenylmethylene dichloride in this way.

[3] See for example, *E. Vogel*, Chem. Ber. *85*, 25 (1952); *P. A. Naro* and *J. A. Dixon*, J. Amer. chem. Soc. *81*, 1681 (1959); *J. Suszko* and *R. Schillak*, Roczniki Chem. *14*, 1216 (1934); *K. Suzuki*, Bull. chem. Soc. Japan *35*, 735 (1962).

Addition of Acetone onto Trinitrobenzene

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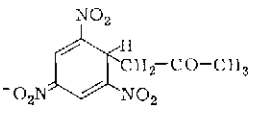
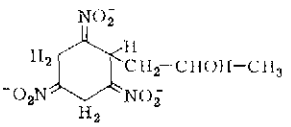
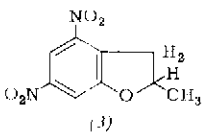
Many polynitro-aromatic compounds give intensely colored salt-like products with compounds containing an acidic C–H group in presence of alkali. Starting from 1,3,5-trinitrobenzene, potassium methoxide, and acetone, *Hantzsch* [1] obtained a black-violet substance, probably of structure *(1)*. However, the formulation *(1)* had not yet been conclusively confirmed despite numerous investigations [2]. Acids effect degradation of *(1)* into the starting components. Nonetheless, *Kimura* [3] was able to isolate picrylacetone by the action of hydrogen peroxide on *(1)*. We have succeeded in ascertaining the position of the acetonyl residue by reduction of the carbonyl group with sodium borohydride. The addition of hydride ions at the aromatic nucleus thereby gives rise to the colorless compound *(2)*.



(1)



(2)



(3)

Compound *(2)* was not isolated but its structure is assured from our previous investigations on reactions of nitroaromatic compounds and sodium borohydride [4] on the one hand, and by the action of bromine on *(2)*, which leads to reoxydation of the nucleus, removal of a nitro group, and ring closure to give 4,6-dinitro-2-methylcoumaran *(3)* on the other; the yield was 35 % based on *(2)*.

Received, March 25th, 1963 [Z 474/302 IE]

[1] *A. Hantzsch* and *N. Picton*, Ber. dtsch. chem. Ges. *42*, 2119 (1909).

[2] *O. Neunhoeffer* et al., Hoppe-Seylers Z. physiol. Chem. *323*, 116 (1961); *R. Foster* and *R. K. Mackie*, Tetrahedron *18*, 1131 (1962).

[3] *M. Kimura*, J. Pharm. Soc. Japan *73*, 1219 (1953).

[4] *T. Severin* and *R. Schmitz*, Chem. Ber. *95*, 1417 (1962); *T. Severin* and *M. Adam*, Chem. Ber. *96*, 448 (1963).

Preparation of Chromium(V) Fluoride and Chromium(VI) Fluoride

By Prof. Dr. O. Glemser, Dipl.-Chem. H. Roesky, and cand. chem. K.-H. Hellberg

Anorganisch-Chemisches Institut der Universität Göttingen (Germany)

When chromium powder is treated with elemental fluorine at 400 °C and 200 atm in a nickel autoclave, bright-red CrF_5 is formed [1], together with a lemon-yellow, unstable product which was identified as CrF_6. By adding small amounts of manganese to the chromium powder, and by using a fluorine pressure of 350 atm, the yield of CrF_6 could be increased to 200 mg per charge.

After heating the autoclave for one hour, the reaction product was condensed in a quartz trap cooled with liquid air. The excess fluorine was removed *in vacuo* leaving the lemon-yellow CrF_6, which decomposes rapidly between −100 and −80 °C *in vacuo* according to the equation

$$(1)\quad CrF_6 \rightarrow CrF_5 + {}^1/_2\, F_2$$

In order to analyse the lemon-yellow product, it was hydrolysed with water in the cold trap. However, it decomposes partially according to equation (1) before complete hydrolysis can occur. Elements other than chromium and fluorine could not be detected.

Quantitative analysis was carried out according to the following hydrolysis equations:

$$(2)\quad 3\, CrF_5 + 7\, H_2O \rightarrow Cr_2O_7^{2-} + Cr^{3+} + 14\, H^+ + 15\, F^-$$

$$(3)\quad F_2 + H_2O \rightarrow 2\, F^- + 2\, H^+ + {}^1/_2\, O_2\, (O_3)$$

The Cr^{VI} was titrated with 0.1 N thiosulfate after adding KI in hydrochloric acid. Then, in a second run, Cr^{III} was oxidized to Cr^{VI} by adding Na_2O_2. The solution was evaporated to dryness, treated with water, and, after addition of HCl and KI, again titrated with 0.1 N thiosulfate. This titration gives

the total amount of chromium present. The amount of fluoride was determined using triphenyltin chloride.

Results:

a) Ratio Cr^{VI}: total Cr
Found 2:3.04; 2:3.00; 2:2.94. Calc. 2:3.

b) Total Cr: total F
Found 1:6.16; 1:6.40; 1:6.25 [2]. Calc. for CrF_6 1:6.

c) For CrF_5
Found Cr:F = 1:4.98; 1:5.10. Calc. for CrF_5 1:5.0.

Elemental fluorine was also detected qualitatively during the decomposition of CrF_6.

Further investigations are in progress.

Received, March 15th, 1963 [Z 468/297 IE]

[1] *H. v. Wartenberg* was the first to obtain CrF_5, albeit in very small amounts: Z. anorg. allg. Chem *247*, 135 (1941); *249*, 100 (1942).

[2] The sample contained traces of HF as an impurity, which could not be removed.

CONFERENCE REPORTS

Biochemical and Clinical Problems in Molecular Genetics

The Deutsche Akademie der Naturforscher LEOPOLDINA organized this symposium on January 26th and 27th, 1963 in Halle/Saale (Germany)

On the first day, problems relating to the role of genetic information in protein synthesis in the cell were dealt with. The lectures on the second day were devoted to clinical problems. It was shown that advancing knowledge of molecular reactions inside the cell provides insight into the pathogenesis of hereditary diseases and in this way leads to a rational therapy.

The Concept Scheme of Molecular Genetics

M. Delbrück, Berkeley, Calif. (U.S.A.) and Köln (Germany)

Molecular genetics attempts to explain the events of heredity on the basis of molecular transformations. To facilitate a better understanding of the lectures on special problems relating to the formation of specific protein molecules, the following concepts were clarified:

Storage of information in deoxyribonucleic acid (DNA) by means of a definite arrangement of nucleotides (triplet code); the importance of the structure of DNA as a double helix – formed by intertwining of two polynucleotide chains and stabilized by hydrogen bonding between the purines and pyrimidines of the two chains – for the replication of DNA and for the relaying of information to messenger ribonucleic acid (m-RNA); juxtaposition of the m-RNA, the matrix for the protein molecule that is to be formed, and the transfer RNA's, which conduct the amino acids to the site of protein synthesis by means of hydrogen bonding between the bases. An anticodon in the transfer RNA must correspond to a codon in the m-RNA.

It was pointed out in the discussion that during the replication of DNA, the double helix need only be partially unwound. It is not yet known how the very long strands of the nucleic acid molecules are handled by the cell.

The Role of the Cell Nucleus in Protein Synthesis and Morphogenesis

J. Brachet, Brussels (Belgium)

In amoebae and *Acetabularia*, the formation of both m-RNA and ribosomal RNA is dependent on the nucleus, since their synthesis ceases immediately after removal of the nucleus. Migration of nucleus RNA into the cytoplasm was demonstrated by labelling experiments. The source of the transfer RNA is still unexplained, as is the question whether chloroplast RNA increases autonomously.

In connection with this problem, the question whether the chloroplasts contain DNA was discussed. It was demonstrated by autoradiography in Professor *Mothes'* Institute that thymidine is incorporated into dividing chloroplasts in young, growing leaves, but not into those of old, fully-grown leaves. The experiments show that the chloroplasts contain DNA that takes part in some metabolic process. It is thus possible that DNA-dependent, nucleus-independent RNA synthesis occurs in chloroplasts.

The nucleus influences protein synthesis indirectly, since in *Acetabularia* the quantity of protein produced only decreases three weeks after removal of the nucleus. m-RNA seems, therefore, to have a considerably longer life-span in *Acetabularia* than in bacteria.

The m-RNA seems to influence morphogenesis, since this process ceases in anucleate halves of *Acetabularia* after RNase treatment, and is inhibited in nucleate halves by actinomycin. However, it has not been elucidated whether the morphogenetic substances are identical with the m-RNA or with a specific, RNA-controlled protein.

The experiments with dividing amphibian eggs demonstrate the importance of an RNA gradient for the differentiation of the egg.

The Morphogenesis of Phages and their Genetic Determinants

E. Kellenberger, Geneva (Switzerland)

The stages of phage synthesis can be ascertained by inhibition with specific inhibitors or by examining mutants. Examination of T_4 mutants showed that at least 50 genes are necessary for the development of the phage. Two groups of genes are distinguished and their arrangement on the chromosomes determined:

1. Genes for the synthesis of the DNA and
2. Genes for the synthesis of the phage proteins.

Smaller groups within these principal groups comprise genes whose function concerns the same phage component. Mutations that block the synthesis of phage-DNA prevent all the genes of the second principal group from functioning. Electron micrographs showed phage fragments that had arisen after blocking of part reactions.

The Chemistry and Biochemistry of Soluble Ribonucleic Acid

H. G. Zachau, Köln (Germany)

Transfer-RNA has the function of conducting activated amino acids to the m-RNA in such a way that the amino acids become attached in an ordered arrangement to the growing peptide chain. It is assumed that m-RNA (matrix) and transfer-RNA (adaptor) are attached to each other in a specific manner by hydrogen bonding between nucleotides

(triplet code). In order to be able to analyse that portion of the transfer-RNA molecule (anticodon) responsible for the attachment, the transfer-RNA specific for each amino acid must be isolated from the mixture of soluble RNA's, for instance by countercurrent distribution of the tri-n-butylammonium salts of the RNA's. After fermentative cleavage of the purified RNA's, their cleavage products can be separated chromatographically and their nucleotide components determined. However, it has not yet been possible to arrange the fragments, so that the structure of the anticodon is still unknown. The structure for enzyme recognition that must be contained in the transfer-RNA is also unknown. Further unsolved questions are: are there twenty or more transfer RNA's and what is the source of the specificity of the transfer-RNA?

Ribosomes and the Molecular Mechanism of Protein Synthesis

A. Gierer, Tübingen (Germany) (communicated by *H. G. Zachau*)

Optimal conditions for synthesis of a protein are only present when several S_{70} ribosomes are bound together by m-RNA into particles of approx. S = 150 (S = sedimentation constant). Even after the addition of synthetic m-RNA, these aggregates show no increase in amino-acid incorporation.

In the discussion, a question was asked about the function of ribosomal RNA. It must not be assumed that it only possesses carrier function and is otherwise inert, since it is clear that a given m-RNA becomes associated with only certain ribosomes.

On the Experimental Analysis of the Amino Acid Code

J. H. Matthaei, Tübingen (Germany)

The sequence of always three nucleotides in m-RNA furnishes the code for the sequences of amino acids in polypeptides. Investigations with mutants prove this. The function of the matrix can be demonstrated in a cell-free system, to which a new m-RNA (virus RNA or polyuridylic acid) is added *in vitro*. In this way, it was possible to obtain information on the coding for amino acids using synthetic polynucleotides as m-RNA. It is not yet known from which end of the polynucleotide chain the code should be read off. Experiments in which trinucleotides were incorporated into m-RNA or were polymerized by polyphosphates by the method due to *Schramm* might be expected to shed light on this problem. It may be assumed that not all codons can exist in neighboring positions. Neighboring bases certainly have some influence on each other.

In the discussion, Prof. *Wacker*, (Frankfurt/M.) pointed out that m-RNA that contains bromouracil instead of uracil is inactive. A code consisting only of purines is resistant to ultraviolet irradiation, while a pyrimidine code is altered by this treatment.

Studies on the Biosynthesis of Tobacco Mosaic Virus

G. Schramm, Tübingen (Germany)

Biosynthesis of the virus requires 30 hours. The chronological sequence of events in this process is: 1. 5–10 h: liberation of the RNA, 2. 10–15 h: growth of the RNA, 3. 3–5 h: growth of the protein, and 4. 5–8 h: production of the high-molecular-weight protein. It has not yet been elucidated whether the RNA synthesis requires the presence of DNA as a primer, or whether the RNA itself can act as primer. The isolation of an RNA polymerase from tobacco leaves makes it possible to carry out an experimental examination of this point. Under the influence of the polymerase, a mixture of purine- and pyrimidine-triphosphates (ATP, GTP, UTP, CTP) is converted principally into oligonucleotides with sedimentation constants S = 1.0–1.5. Only about 0.2% of the reaction product has a higher molecular weight and is found in the same fraction as TMV-RNA. The content of polymerase is the same in healthy and in TMV-infected leaves. TMV-RNA is destroyed by polymerase from healthy leaves on account of its RNase content. However, TMV-RNA that is mixed with polymerase from infected leaves is not degraded but, on the contrary, increases in activity. On the basis of these results, attempts can be made to prepare an informative RNA *in vitro*.

Polynucleotide Synthesis in Coacervate Drops

A. I. Oparin, Moscow (SSSR)

Polymers such as polypeptides or polynucleotides can associate together to form complexes, which are demarcated from the external medium but which enter into reciprocal exchange with the surrounding solution and which selectively absorp material from it against concentration gradients. According to *Oparin*, during the course of terrestrial history, corresponding coacervates were subjected to selection, which led to adaptation to environmental conditions and to evolution of complex systems. These complexes had to be self-reproducing.

Experiments have shown that RNA in a coacervate drop is broken down by RNase and that a coacervate drop containing polynucleotide phosphorylase abstracts ADP from the external solution and converts it into polyadenylic acid. In the discussion, Prof. *Schramm* pointed out that the formation of the first matrix is the decisive factor in the origin of self-propagating complexes and thus for the possibility of evolution. In his studies on non-enzymatic syntheses of nucleic acids, it had been shown that polyadenylic acid can act as a matrix and accelerate the formation of polyuridylic acid and vice versa. The basic question is therefore: how has the information entered into the macromolecules?

The Molecular Structure of Haemoglobin and its Modification

G. Braunitzer, Munich (Germany)

The primary structure (amino-acid sequence) of human haemoglobin has been completely elucidated. The secondary, tertiary, and quaternary structures have been examined by means of X-ray analysis, which has made it possible to derive relationships between the amino-acid units and the spatial construction. The α- and β-chains of haemoglobin and the myoglobin chain all show great similarities in spatial construction, although, in the helical regions, numerous amino acids are not possessed in common by the several chains and are therefore not interchangeable. However, some amino acids occupy the same positions in all chains. Proline is generally present where there are kinks in the chains.

If only one amino acid in the α- or β-chain of haemoglobin is exchanged for another, an anomalous haemoglobin is formed that gives rise to symptoms of disease. Thus, in the β-chain of sickle cell haemoglobin, for instance, glutamic acid has been replaced by valine. If a cysteine is oxidized at the site far away from this glu-val exchange, then sickle cells do not arise. No explanation has yet been deduced for this behaviour. By means of the model, it can be seen that the oxidizability of the iron in the haem is altered by exchanging histidine for tyrosine and valine for glutamic acid at a certain position in the chain but not, on the other hand, by replacement of histidine with arginine.

The Pathological Importance of Haemoglobin Anomalies

K. Betke, Tübingen (Germany)

Haemoglobin anomalies are gene-dependent. The pathological symptoms generally become apparent only when the anomaly is inherited homozygously. Normal human haemo-

globin consists of > 95% HbA, 2% HbA_2, and 0.5% HbF. This composition is altered by anomaly of the α- or β-chains in HbA, since as a replacement for the defective chains, δ (HbA_2) and γ (HbF) chains are incorporated. Pathological manifestations can be associated with definite changes in the composition of the haemoglobin.

Biochemistry and Pathogenesis of Hereditary Haemolytic Anaemias with Enzyme Defects in the Hexose Monophosphate Cycle

G. W. Löhr and *H. D. Waller*, Tübingen (Germany)

There are two haemolytic anaemias that are caused by enzyme deficiencies in the hexose monophosphate cycle:

1. Glucose-6-phosphate dehydrogenase deficiency, the most frequent hereditary disease. The life-span of the erythrocytes is shortened. In general, haemolysis only occurs after administration of drugs (*e.g.* primaquine, a derivative of 8-aminoquinoline).

2. Glutathione reductase deficiency, first observed 1961/1962. The haemolytic crises appear spontaneously.

Metabolism in Hereditary Enzymopathies

F. Linneweh, Marburg/Lahn (Germany)

The following diseases due to enzyme defects were discussed:

1. Phenylketonuria: Blocking of the breakdown of phenylalanine to tyrosine leads to excretion of phenylpyruvic acid. Since the amino acid pool becomes unbalanced as a result of an excess of intact phenylalanine, resorption in the gut is decreased. For this reason, the supply of essential amino acids to the brain is reduced, this in turn leading to mental deficiency if it occurs during the phase of brain differentiation in the infant. By administration of a diet low in phenylalanine in the first year of life, such children could develop normal intelligence.

2. Cystinosis is due to disturbance of the breakdown of cysteine to taurine and the toxic effect of the intermediate product on the kidney.

3. Leucinosis: The lack of a decarboxylase prevents catabolism of leucine, isoleucine, and valine.

4. Glycogenosis: There is a deficiency of glucose-6-phosphatase.

[VB 687/79 IE]

Kinetics of the Thermal Decomposition of Magnesium and Calcium Carbonates

E. Cremer, Innsbruck (Austria)

The rates of decomposition of $MgCO_3$ [1] and $CaCO_3$ [2] are strongly dependent on the CO_2 pressure, even in a temperature and a pressure range in which the reverse reaction could certainly not yet be observable. The oxides had to be decomposed at constant pressure in order to determine the "order" of the reaction. The concept of order in heterogeneous reactions, however, poses certain problems. What one measures here is generally the change of percentage conversion (u) with time, and the equation

$$-d(100-u)/dt = k(100-u)^n$$

applies formally, just as for gas reactions. For a gas reaction however, (100−u) is proportional to the concentration in the entire reaction volume, whereas for the heterogeneous reaction, generally only a fraction of (100−u) % may have the opportunity of reacting simultaneously. If the reaction rate is proportional to the surface area of the starting material, as is the case with $CaCO_3$ prepared from CaO and CO_2 [2], then $n = {}^2/_3$ in the above reaction. The data from measurements of the decomposition of $MgCO_3$ are better evaluated by a diffusion formula (for low conversion $u^2 = kt$) [1]. However, the diffusion through the oxide film formed is certainly not rate determining [3]. The rate coefficient k, which is independent of the degree of decomposition, can be used to evaluate the pressure and temperature dependence of the reaction. The induction period due to the formation of reaction nuclei observed in the decomposition of $CaCO_3$ can be eliminated by preforming the nuclei during preparation. For the pressure dependence of the CaO formation reaction at 800–850 °C we have,

$$k = k^* (1/p_{CO_2} - 1/p_x)$$

This relationship can be derived theoretically if the establishment of a surface equilibrium $CaCO_3 \rightleftarrows CaO^* + CO_2$ is assumed, where p_x denotes the equilibrium pressure above the reacting mass. The equilibrium pressure with $MgCO_3$ is so high at 500–600 °C that the term $1/p_x$ can be neglected.

The pressure dependence of k can be written:

$$k = k^* (1 + bp_{CO_2})/p_{CO_2}$$

This relationship can be deduced from the same factors as with the decomposition of $CaCO_3$, but with the assumption of stronger CO_2 adsorption.

[GDCh-Ortsverband Frankfurt/Main (Germany), February 7th, 1963] [VB 685/75 IE]

Unimolecular Reactions in Photochemical Systems

G. B. Porter, Frankfurt/Main (Germany) [4]

Our studies of the dependence of pressure, temperature, and wave length of the quantum yields of photolysis of gaseous hexafluoroacetone show that there are two alternative primary processes. One involves monomolecular dissociation of excited singlet state molecules, which are formed with vibrational energy considerably in excess of the equilibrium energy during the excitation process with light. The fact that the quantum yields decrease with increasing pressure can be interpreted in terms of competition between dissociation and collisional degradation. The quantum yields also decrease at long wave lengths, because the excited singlet molecules are formed with low vibrational energy. The temperature of the system has little effect on this primary process, since it affects only the equilibrium vibrational energy of molecules.

The second primary process entails unimolecular dissociation of triplet state molecules formed from excited singlet state molecules by intersystem crossing in a radiationless transition. Since the triplet state has a relatively long lifetime (*ca.* 10^{-4} sec) there is ample time for vibrational equilibrium to be established. Thus, this primary process is essentially a thermal unimolecular reaction. As such, its rate constant depends strongly on temperature, but not on the wave length of excitation. Added biacetyl accepts energy efficiently from hexafluoroacetone triplet state molecules, completely deactivating them to the ground state. Even traces of biacetyl eliminate the second mode of dissociation almost completely, which permits the two primary processes to be studied independently.

[GDCh-Ortsverband Freiburg-Südbaden (Germany), February 8th, 1963] [VB 686/74 IE]

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[1] *E. Cremer, K. Allgeuer*, and *W. Aschenbrenner*, Radex-Rundschau *1953*, 494.

[2] *W. Nitsch*, Ph. D. thesis, Universität Innsbruck 1959; *E. Cremer* and *W. Nitsch*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *66*, 697 (1962).

[3] *L. Bachmann* and *E. Cremer*, Z. anorg. allg. Chem. *65*, 309 (1961).

[4] Present address: Institut für physikalische Chemie der Universität Frankfurt/Main. Work carried out in collaboration with *P. Bowers*, University of British Columbia, Vancouver (Canada).

Diboron, Polyboron, and Metal-Boron Compounds

H. Nöth, Munich (Germany)

Diboron compounds B_2X_4 are readily accessible by dehalogenation of boron chlorides X_2BCl provided at least one of the ligands X in X_2BCl is a dimethylamino group:

$$2\,X[(H_3C)_2N]BCl + 2\,K \rightarrow X[(H_3C)_2N]B{-}B[N(CH_3)_2]X + 2\,KCl \quad (a)$$

$X = N(CH_3)_2$, CH_3, C_2H_5, C_3H_7, C_6H_5, OR, or PR_2

All diboron compounds tend to disproportionate as follows:

$$B_2X_4 \rightarrow BX_3 + \frac{1}{x}(BX)_x \quad (b)$$

Stability increases along the series X = Cl, OR, NR_2. Disproportionation of mixed diboron compounds proceeds in a somewhat more complex manner than that according to (b), but here, too, boron(III) and polyboron compounds are always formed. The increase in stability in the series B_2Cl_4, $B_2H[N(CH_3)_2]_3$, $B_2(OCH_3)_4$, $B_2R_2[N(CH_3)_2]_2$, $B_2R[N(CH_3)_2]_3$, $B_2Cl_2[N(CH_3)_2]_2$, $B_2[N(CH_3)_2]_4$ demonstrates the stabilizing influence of the $N(CH_3)_2$ group, which is of both electronic and steric nature. A mechanism is proposed for the course of the disproportionation which leads to polyboron compounds via boron compounds with chain-structures.

In parallel with thermal stability, there is also a decrease in reactivity of the B–B bond. $B_2[N(CH_3)_2]_4$ cannot be hydrogenated even at 200 °C/200 atm while $B_2Cl_2[N(CH_3)_2]_2$ is hydrogenated to $[HBClN(CH_3)_2]_2$ already at 100 °C/50 atm. Reaction of HCl with $B_2[N(CH_3)_2]_4$ leads to $B_2Cl_4{\cdot}2HN(CH_3)_2$ *via* $B_2Cl[N(CH_3)_2]_3$ and $B_2Cl_2[N(CH_3)_2]_2$. The dichloro-derivative can also be prepared from 1 mole of BCl_3 and 1 mole of $B_2[N(CH_3)_2]_4$. If the stabilizing influence of the $N(CH_3)_2$ groups is absent in substitution reactions, disproportionation occurs along with substitution. Thus, when HCl, BF_3, and ROH interact with $B_2R_2[N(CH_3)_2]_2$, RBX_2 and (BR) are obtained, but not the diboron compounds $B_2R_2X_2$ (X = Cl, F, or OR). The decomposition of the diboron compounds offers the best method available at present for the preparation of polyboron compounds.

The stabilizing effect of the $N(CH_3)_2$ group makes it possible to synthetize dimethylaminoboron compounds with chain structures, *i.e.* the homologous series $B_n[N(CH_3)_2]_{n+2}$; so far, members up to n = 6 have been isolated.

Attempts to produce boron-lithium, boron-magnesium, and boron-mercury compounds have proved unsuccessful. Boron-metal bonds have, however, resulted from reaction of sodium carbonylometallates with boron chlorides.

[Anorganisch-chemisches Institut, Universität Göttingen (Germany), February 18th, 1963]

[VB 691/81 IE]

Tetrahydrofuran-3-one, Spiranes, and Bithienyls

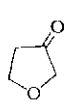
H. Wynberg, Groningen (Holland)

1. Tetrahydrofuran-3-ones

Three synthetic routes leading to compounds of this type have been developed:

a) Greatly improved oxidation [1] with chromic acid or pyridine/chromic oxide of the corresponding 2-, 4- or 5-substituted 3-hydroxytetrahydrofurans furnishes *(1)* in yields of up to 70 %.

(1)



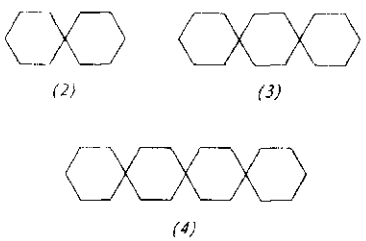
[1] *Yu. K. Yur'ev*, *E. M. Lukina*, and *I. K. Korobitsyna*, Zhur. obsh. Khim. *24*, 1238 (1954); Chem. Abstr. *49*, 12430 (1955); *H. Wynberg*, J. Amer. chem. Soc. *80*, 364 (1958).

b) Acid-catalysed cyclization [2] of β-alkoxydiazoketones yields 2-methyl- (5 %), 4-methyl- (41 %), and 5-methyl- (30 %) tetrahydrofuran-3-ones.

c) Base-catalyzed cyclization [3] of β-oxa-adipoyl chloride leads *via* the diketene to 3-keto-4(2)-ethoxycarbonyltetrahydrofuran, which on hydrolysis and decarboxylation gives *(1)* in 45 % yield.

2. Spiranes

Monospiro[5,5]undecane *(2)* dispiro[5,2,5,2]hexadecane *(3)*, m.p. 84 °C and trispiro[5.2.2,5,2,2]heneicosane *(4)*, m.p. 158 °C, can be prepared in reasonable yields by reduction of

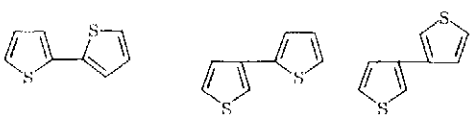


(2) *(3)* *(4)*

the ketones obtained from a double Michael condensation between divinyl ketone and 1,3-cyclohexadiones [4], or by a dialkylation reaction of cyclohexanones [5]. The protons of the outer- and inner rings in *(3)* and *(4)* show τ-values of 8.65 and 8.75 respectively.

3. Dithienyls

The dipole moments of 2,2′-dithienyl *(5)*, 2,3′-dithienyl *(6)*, and 3,3′-dithienyl *(7)* were found to be 0.77, 1.07, and 0.75 D, respectively, in benzene solution.



(5) *(6)* *(7)*

It appears that in *(5)* and *(7)*, the rings are preferentially at nearly 90 ° to one another [6], while in *(6)*, coplanarity is the predominant conformation.

[GDCh-Ortsverband Frankfurt/Main (Germany)
February 21st, 1963]

[VB 693/80 IE]

Photochemical Reactions with Transition Metal Carbonyls

W. Strohmeier, Würzburg (Germany)

If a solution of a metal carbonyl or a metal carbonyl derivative is irradiated with ultraviolet light in the presence of an electron donor D, carbon monoxide is split off photochemically according to equation (a)

$$YM(CO)_x + :D + h\nu \rightarrow YM(CO)_{x-1}D + CO \quad (a)$$

and the donor is substituted in the vacant orbital on the metal carbonyl. Suitable electron donors are, "n"-donors

[2] *H. E. Sheffer* and *J. A. Moore*, J. org. Chemistry *28*, 129 (1963).

[3] *J. C. Sauer*, J. Amer. chem. Soc. *69*, 2448 (1947).

[4] *H. A. P. de Jongh* and *H. Wynberg*, Recueil Trav. chim. Pays-Bas *82*, 202 (1963).

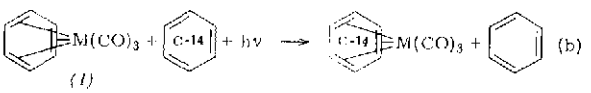
[5] *M. Mousseron*, *R. Jacquier*, and *H. Cristol*, Bull. Soc. chim. France *1957*, 346.

[6] *A. Almenningen*, *D. Bastiansen*, and *P. Svendsås*, Acta chem. scand. *12*, 1671 (1958).

containing a functional atom in the form of an element from group V or VI of the periodic table, or "π"-donors such as ethylene or acetylene derivatives and cyclic dienes. The stability of the derivatives obtained with "π"-donors depends on the strength of the D compound as donor and not on its basicity. With bifunctional donors D–R–D, in which the donor atoms are contained in a ring system, as for instance with piperazine, poly-nuclear metal-carbonyls $YM(CO)_{x-1}$–D–R–D–$(CO)_{x-1}MY$ are obtained, the donor D–R–D acting as ligand.

If an arene metal tricarbonyl $ArM(CO)_3$ *(1)* is dissolved in an aromatic solvent Ar* which is labelled with ^{14}C and irradiated, exchange of the ligand Ar is photochemically induced according to (b).

The "π"-bond between Ar and the central atom in *(1)* is ruptured photochemically. The intermediate product $\{M(CO)_3\}$ then recombines with Ar* to give $Ar^*M(CO)_3$.



(1) (b)

The three localized bonds between cyclopentatriene and the central atom in cyclopentatriene metal carhonyls are also opened photochemically.

[GDCh-Ortsverband Ruhr (Germany), March 13th, 1963]

[VB 692/82 IE]

SELECTED ABSTRACTS

Utilization of hydrogen produced during electrolysis of alkali chlorides for producing ammonia has been achieved in a plant erected by the Österreichische Stickstoffwerke in Sweden. The daily output is 5–15 tons of ammonia. Hydrogen formed during electrolysis of alkali chlorides according to the equation:

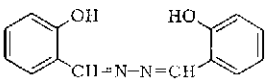
$$NaC_{(aq)} + H_2O \longrightarrow NaOH_{(aq)} + \tfrac{1}{2}H_2 + \tfrac{1}{2}Cl_2$$

has so far been used for producing hydrogen chloride, for heating, for hydrogenation, or simply flared off. This hydrogen can be utilized economically and successfully as raw material for ammonia production. If the hydrogen constitutes a very high proportion of the production costs for ammonia, only plants with a minimum capacity of 200–300 tons of ammonia per day are economical. Ammonia production of 5–6 tons per day can be of interest if the hydrogen used is a hitherto unused by-product, such as occurs with alkali chloride electrolysis. The nitrogen required for the ammonia synthesis can be obtained from an air fractionation plant or from air by burning or cracking liquid or gaseous hydrocarbons in it. If no other nitrogen source is available, production of nitrogen by burning part of the hydrogen in air is most economical. The plant consists of a low pressure and a high pressure section. The low pressure section comprises a gas holder for storing the hydrogen and synthesis gas, the equipment for producing or purifying the nitrogen and the conveyor system. The high pressure plant consists of a high pressure compressor, a high pressure recirculating compressor, the synthesis converter, a refrigeration plant, and possibly a storage vessel for liquid ammonia. The yield of ammonia based on the hydrogen/nitrogen mixture supplied by the high pressure compressor is at least 90 %, even for plants with capacities of only 5 tons per day. The power consumption per ton of ammonia produced is generally less than 1500 kWh. / *H. Hinrichs* and *J. Niedetzky*, Chemie-Ing. Techn. *34*, 819 (1962) / –Gr [Rd 133/IE]

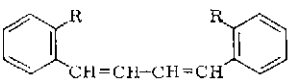
Ring enlargements of acenaphthenequinones with diazoalkanes were studied by *B. Eistert* et al. and by *A. Schönberg* and *G. Schütz*. Compounds of the phenalene series are formed. Diazoethane and phenyldiazomethane are particularly suitable. The products are not 2-methyl- or 2-phenyl-1,3-dioxo-2,3-dihydrophenalenes, which are already known, but instead enolized 1,2-diketones substituted in the 3-position: 1-oxo-2-hydroxy-3-methylphenalene, orange-red needles, m.p. 190 to 191 °C, or 1-oxo-2-hydroxy-3-phenylphenalene, brown-red crystals, m.p. 179–181 °C. In contrast to the β-diketones, which are fixed in the *trans*-configuration, these compounds give color reactions with $FeCl_3$, and form sparingly soluble, chelated copper complexes. The diazo carbon atom therefore does not enter between the two CO groups, but, as with isatin, between one CO group and the aromatic residue. / Chem. Ber. *95*, 2416 (1962) / –W. [Rd 423/120 IE]

Organometallic compounds of aluminum with acetylene and its homologues are described by *P. Chini*, *A. Baradel*, *E. Pauluzzi*, and *M. De Maldè*, who discuss the methods of preparation: 1) from alkali metal acetylides and $AlCl_3$, 2) from alkyl-mercury or aryl-mercury acetylides and metallic Al, 3) from alkyl-mercury or aryl-mercury acetylides and $AlH_3{\cdot}N(CH_3)_3$, and 4) from acetylenic hydrocarbons and $LiAlH_4$. The syntheses with AlH_3 lead to partial hydrogenation of the triple bond. Depending on the starting material, either $Al(C{\equiv}CH)_3{\cdot}X$ or $Al(C{\equiv}C{-}R)_3{\cdot}X$ is obtained, where X = dioxan, tetrahydrofuran, trimethylamine, or pyridine and R = CH_3, C_4H_9, or C_6H_5; alternatively, double complexes such as $Li[Al(C{\equiv}CH)_4]{\cdot}C_4H_8O$ or $K[Al(C{\equiv}CH)_3F]$ are formed. The compounds of the type $Al(C{\equiv}CH)_3{\cdot}X$ are sublimable and are oxidized by air (without igniting) and react very violently with water and alcohol. Very slight ethynylation occurs with acetone. The non-explosive compounds detonate when the second component of the complex is removed. / Chim.e L'Ind. *44*, 1220 (1962) / –Pf. [Rd 478/131 IE]

Fluorescent aromatic azines. Aromatic azines of the salicylaldazine type *(1)* fluoresce in the visible region of the spectrum on irradiation of the solid substances or their solutions in toluene with ultraviolet light. The fluorescence is attributed to the formation of intramolecular hydron egbridges. *O. Westphal* et al. have investigated the absorption and fluorescence spectra of aromatic azines and a number of butadiene derivatives *(2* and *3)*. The capacity of aromatic azines to fluoresce depends on the degree of protonation of the azine group; the unusually large Stokes' shift of compounds substituted by hydroxyl groups in the *o*-position to the azine group is ascribed to an intramolecular proton transition in the excited electronic state. Conventional processes are suitable for the preparation of symmetric azines. Asymmetric azines are obtained by treating hydrazones with anils of aldehydes in absolute solvents, or – provided the hydrazones used are stable, *e.g.* with the hydrazone of 2,2'-dihydroxybenzophenone or with 2,2'-dihydroxybenzil dihydrazone – by direct reaction with the corresponding aldehydes and ketones. 1,4-Bis-(*o*-hydroxyphenyl)buta-1,3-diene *(2)* can be prepared by conversion of (2-hydroxyphenyl)acetylene into the diacetylene derivative and partial hydrogenation of the latter. 1,4-Bis-(*o*-methoxyphenyl)buta-1,3-diene *(3)* can be obtained by treating 2-methoxybenzaldehyde with acetylenedimagnesium bromide, partially hydrogenating the resulting acetylenic glycol, and finally eliminating the hydroxyl groups with P_2I_4 in ether. / Liebigs Ann. Chem. *657*, 39, 52, 64 (1962) / –Wf. [Rd 414/129 IE]

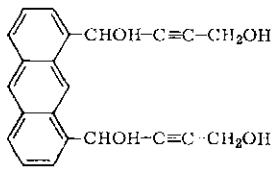


(1)



(2): R = –OH
(3): R = $-OCH_3$

A cyclic octa-acetylene, containing two anthracene systems, was synthetized by *S. Akiyama, S. Misumi,* and *M. Nakagawa.* Dimethyl 1,8-anthracenedicarboxylate was reduced to 1,8-di(hydroxymethyl)anthracene with $LiAlH_4$. Oxidation of this with CrO_3 in pyridine yielded anthracene-1,8-dicarboxaldehyde *(1)*. Reaction of *(1)* with the lithium salt of tetrahydropyranyl propargyl ether, followed by hydrolytic fission of the tetrahydropyranyl group led to the tetraol *(2)*. Treatment with $SOCl_2$ yielded the tetrachloride, and dehydrochlorination with sodium in liquid ammonia gave 1,8-di(butadiynyl)anthracene*(3)*. On oxidative coupling with copper acetate in pyridine at 20 °C, *(3)* was converted into the



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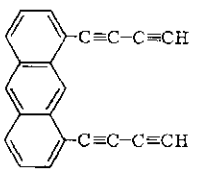

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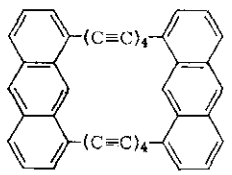

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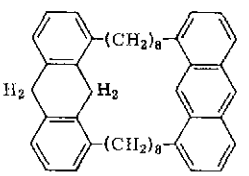
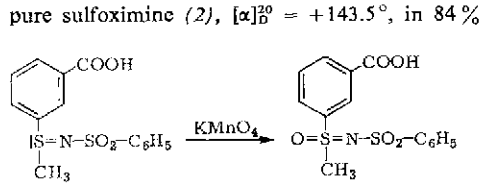


(5)

octayne compound *(4)*, which forms red needles and is reasonably stable. Catalytic hydrogenation converts *(4)* into a hydrocarbon $C_{44}H_{50}$, which has the probable structure *(5)*. / Bull. chem. Soc. Japan *35*, 1829 (1962) / –Ko [Rd 476/136 IE]

A synthesis of ketones from acid chlorides and aluminum alkyls was investigated by *H. Bertsch* and *H. Reinheckel.* A series of aliphatic and aromatic acid chlorides can be converted into ethyl ketones in 80–85 % yield by treatment with ethylaluminum sesquichloride, a 1:1 mixture of diethylaluminum chloride and ethyl aluminum dichloride in aliphatic hydrocarbons such as pentane, hexane, or heptane, cooled with ice. All ethyl groups of the reagent are utilized. Alkoxycarbonylalkylcarbonyl chlorides give ketonic fatty acids in good yield. Ethylaluminum dichloride behaves like the sesquichloride, but diethylaluminum chloride gives less satisfactory, and triethylaluminum even worse yields. Examples: 3-hexanone, b.p. 120–123 °C, 81 %; 3-decanone, b.p. 91–93 °C/15 mm, 80 %; 3-tetradecanone, b.p. 142 to 145 °C/10 mm, 84 %; eicosanone, b.p. 155–157 °C/0.03 mm, 82 %; propiophenone, b.p. 95 °C/13 mm, 80 %; methyl 10-ketolaurate, b.p. 175 °C/11 mm, m.p. 23.5–24.5 °C, 92 %. / Fette, Seifen, Anstrichmittel. Ernährungsind. *64*, 881 (1962) / –Ma. [Rd 474/134 IE]

Oxidation of sulfimines to sulfoximines with alkaline permanganate solution is completely stereospecific according to *G. Kresze* and *Brigitte Wustrow.* The optically pure sulfimine *(1)*, $[\alpha]_D^{20} = +254°$, can be converted into the equally optically pure sulfoximine *(2)*, $[\alpha]_D^{20} = +143.5°$, in 84 % yield. The

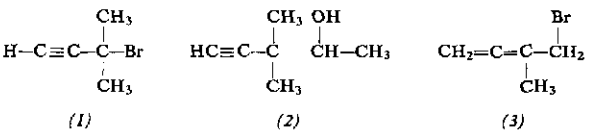


(1) *(2)*, Yield 84%

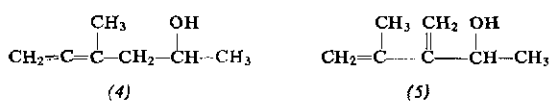
optical purity of *(2)* was proved by resolution of racemic *(2)* with optically active α-phenylethylamine and recrystallization from methanol. The final rotation of the two stereoisomers was found to be $[\alpha]_D^{20} = \pm 143.5°$. Investigation of the rotatory dispersion indicates that the configuration is not changed during the reaction. / Chem. Ber. *95*, 2652 (1962) / –Ko. [Rd 475/135 IE]

Vanadium hexacarbonyl reacts with cycloheptatriene at 50 °C to form a microcrystalline, red-brown, paramagnetic substance insoluble in water and hydrocarbons. This has been identified as the hexacarbonylvanadate of vanadium(0)-π-tropylium-π-cycloheptatriene, $[V(C_7H_7)(C_7H_8)]^+[V(CO)_6]^-$. The cation $[V(C_7H_7)(C_7H_8)]^+$, which was also isolated as its tetraphenylborate, is the first example of a structure in which two C-rings are bound together through a continuous π-electron system over a bridging transition metal. Since $V(C_7H_7)(CO)_3$ is formed as a by-product, the reaction presumably proceeds via $V(C_7H_8)(CO)_3$ with elimination of a hydrogen ion. / Chim.e L'Ind. *44*, 1217 (1962) / –Pf. [Rd 479/132 IE]

Solutions in ether of α-ethynyl- and α-allenyl-alkylmagnesium halides were obtained by *Y. Pasternak,* by irradiating the Mg throughout the reaction with a tungsten lamp or daylight



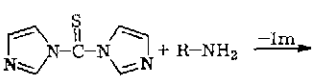
(1) *(2)* *(3)*



(4) *(5)*

reflected from a mirror. The Grignard compound of *(1)* gave *(2)* on treatment with acetaldehyde, and the organo-magnesium compound of *(3)* resulted in a mixture of *(4)* and *(5)* in 50 % yield. The infrared spectra and hydrolysis of the organometallic compounds showed that the formation of the Grignard compounds is accompanied by a propargyl → allene or an allene → diene rearrangement. On treatment with the aldehyde, the corresponding retro-rearrangement takes place. / C. R. hebd. Séances Acad. Sci. *255*, 1750 (1962) / –Bs. [Rd 480/138 IE]

A new synthesis of isothiocyanates has been developed by *H. A. Staab* and *G. Walther. N,N'*-Thiocarbonyldiimidazole *(1)*, which is obtained in good yield from thiophosgene and imidazole, forms imidazole-1-thiocarboxamides *(2)* with 1:1 molar ratios of primary aliphatic and aromatic amines at room temperature; the amides then dissociate at room temperature into imidazole and the corresponding isothiocyanate *(3)*. Typical yields are: phenylisothiocyanate, 78 %;



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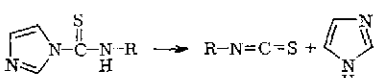
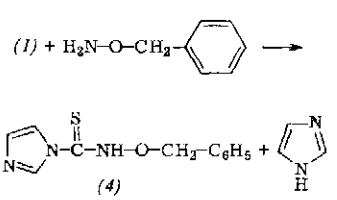


(2) *(3)*

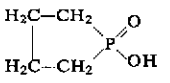
cyclohexylisothiocyanate, 72 %; and n-butylisothiocyanate, 77 %. Reaction of *(1)* with secondary amines does not proceed beyond the imidazole-1-thiocarboxamide stage. Reaction between *(1)* and *O*-benzylhydroxylamine yields the fairly stable *N*-benzyloxyimidazole-1-thiocarboxamide *(4)*.



(4)

There was no evidence for dissociation of *(4)* into the expected benzyloxyisothiocyanate and imidazole. / Liebigs Ann. Chem. *657*, 104 (1962) / –Ko. [Rd 477/137 IE]

Tetramethylenephosphinic acid *(1)* was synthetized by *B. Helferich* and *E. Aufderhaar*. 1-Chloro-4-bromobutane was converted into the organo-cadmium compound, which on treatment with PCl_3 gave rise to 4-chlorobutyldichlorophosphine *(2)* plus some 1,8-dichlorooctane *(3)*. If the mixture of *(2)* and *(3)* is treated with an alcohol and a tertiary amine, *e.g.* ethanol and dimethylaniline, or n-butanol and pyridine, *(2)* is converted into a dialkyl 4-chlorobutylphosphonate. An



(1)

intramolecular Michaelis-Arbusov reaction converts this into an alkyl chloride and an alkyl tetramethylenephosphinate, hydrolysis of which yields the free acid *(1)*. The latter crystallizes as colorless needles, m. p. 53–54 °C. / Liebigs Ann. Chem. *658*, 100 (1962) / –Ko. [Rd 419/119 IE]

Cyclohepta-1,3-diene and its substitution products result when alkali metals or organo-alkali metal compounds add onto tropilidene, according to *K. Hafner* and *W. Rellensmann*. In liquid NH_3, the triene adds on two atoms of sodium in the 1- and 6-positions to form a red cyclopeptadiene dianion which is converted by ammonolysis into 5-cyclohepta-1,3-dienylsodium, even at –50 °C. With alkyl halides, this gives 5-alkylcyclohepta-1,3-dienes and also yields cyclohepta-1,3-dienes in 80–90% yield with NH_3 or amines at 20 °C. In ether, tropilidene is immediately converted into the conjugated diene (60%) with sodium in the presence of metallation mediators (*e.g. N*-methylaniline). Alkyl-lithium compounds also add onto tropilidene at the 1- and 2- or 1- and 6-positions, depending on the alkyl residue, to give alkylcyclohepta-1,3-dienyllithium compounds which are easily converted into the corresponding substituted cyclohepta-1,3-dienes or tropilidene. / Chem. Ber. *95*, 2567 (1962) / –Ha. [Rd 418/130 IE]

BOOK REVIEWS

Die ätherischen Öle (Essential Oils), Vol. IIIa, by *E. Gildemeister* and *F. Hoffmann*. Akademie-Verlag, Berlin 1960. 4th Edit., XV, 628 pp., 3 figures, 64 tables. Clothbound, price DM 63.– (about $ 16.–).

The present volume IIIa [1] forms the first part of the third volume which deals with the compositions of essential oils and which is of primary importance to the terpene chemist. The arrangement of subject matter remains essentially the same as in previous editions. Here, too, the steam-volatile constituents are again chiefly described. Slightly volatile or non-volatile diterpenes and triterpenes are, however, also dealt with, partly with reference to the relevant literature. In this volume IIIa, hydrocarbons (aliphatics, polyprenes, aromatics, and indefinite compounds) and some of the alcohols up to and including acyclic monoterpene alcohols are discussed. It is a pity that the chapter on alcohols had to be divided between the two parts IIIa and IIIb.

In the introduction to polyprene hydrocarbons, the chapter on physical methods is indeed sadly inadequate in view of their great importance for elucidating the constitutions and conformations of terpenes. Thus, for example, the old Auwers-Skita rule is still mentioned instead of the new one which replaces the often incorrect allocation into geometric isomers by the correctly founded concept of conformational stability. Furthermore, there is no mention of rotatory dispersion and mass spectrography. It is also incorrect to denote axial groups as polar groups (p. 21) since this notation has long been discontinued. On the other hand, the subject of the composition of essential oils appears to have been dealt with in full, with the exception of the very latest research advances. Occasional treatment of stereochemical data in clearly drawn structural formulae is commendable. What should be of particular interest to the research worker is the compilation of polyprene hydrocarbons of unknown structure.

The book is heartily recommended to all friends of the old '*Gildemeister*', since it closely follows the tradition of its predecessor despite the completely new revision.

Max Stoll, Geneva [NB 998/42 IE]

Les Cyclitols, Chimie, Biochimie, Biologie, (The Cyclitols, their Chemistry, Biochemistry, and Biology) by *Theodore Posternak*, from the series "Chimie des Substances Naturelles" (Chemistry of Naturally Occurring Substances), edited by *E. Lederer*. Hermann Cie., Paris, 1962, 1st Edit. 492 pp., numerous illustrations, bound. Price NF 48.–. (about $ 12.–).

In the series "Chimie des Substances Naturelles" edited by *E. Lederer* the volume on the cyclitols by *Th. Posternak* is now available.

The book is divided into two sections. In the first, a comprehensive survey of the chemistry of the cyclitols is given, in which not only naturally occurring compounds in this series but also those obtained only by synthetic methods are considered. After an introduction on questions of the nomenclature, configuration, and general reactions of the cyclitols, the chemistry of *myo*-inositol is discussed; its syntheses and chemical and microbiological reactions are described in detail; some preparative and analytical references and physical data complete the treatise. In the following chapters, the author deals in a similar manner with the remaining inositols, cyclohexanepentols, inositol-*o*-methyl ethers, cyclopentane- and cyclohexane-tetrols and-triols, and the conduritols. Later chapters are concerned with aminocyclitols, phosphoric esters of cyclitols, quinic acid, shikimic acid, and numerous other derivatives of the cyclitols. Over 700 literature references to publications up to about 1960 are given.

The second part of the book is entitled: Biochemistry and Biology of the Cyclitols. The author deals *inter alia* with: the natural occurrence and biosynthesis of the cyclitols; the metabolism and physiological importance of *myo*-inositol and phytic acid in the animal organism, microorganisms, and plants; lipoids containing inositol, and the biosynthesis of aromatic compounds with shikimic acid as key substauce. This section is also provided with numerous literature references.

The book presents an excellent survey of the present position of our knowledge from the pen of an expert to whom this special field of research is indebted for several outstanding and fundamental impulses. Of all the monographs on cyclitols that have appeared in recent years, this book is the only one that can make any claim to completeness, so that it may be recommended to organic chemists and biochemists who are interested in this field and who have a command of the French language. The extensive author and subject index facilitates searches into certain branch subjects. The numerous, clearly arranged formulae illustrations should also be noted. Unfortunately the book is not very durably bound.

K. Heyns [NB 5/41 IE]

Namenreaktionen. Ein Beitrag zur Terminologie der organischen Chemie, Biochemie und theoretisch-organischen Chemie. (Name Reactions. A Contribution to the Terminology of Organic Chemistry, Biochemistry, and Theoretical Organic Chemistry.) By *H. Krauch* and *W. Kunz*. Dr. Alfred Hüthig Verlag, Heidelberg, 1961. 1st Edition, VIII+ 592 pp., DM 46.– (about $11.50).

The incentive for creating this work was given by *Richard Kuhn*, and maintained by the interest of the late editor of Beilstein's Handbook, *Friedrich Richter*, who wrote in his foreword to the book: "this encyclopaedic review has in

[1] Vol. IV see Angew. Chem. *68*, 720 (1956).

reality become a textbook of the most important organic reactions, and of their mechanisms, as accepted at present". The authors claim more modestly "that the present volume is to be regarded as a mere attempt to begin a systematic development of terminology describing and defining organic reactions". Their object has been successfully achieved.

The reviewer is particularly impressed with this aim of the authors: "in order to increase the amount of information derivable from each term, . . . these will be accompanied by explanatory notes in an easily memorizable form". Thus, we no longer hear of simply "Bredt's rule", but of "Bredt's bridgehead double bond rule", while the Clemmensen reaction appears as the "Clemmensen carbonyl → methylene reduction".

This terminology based on the name of the discoverer(s) plus the subject matter is practically indispensible when it is remembered that Emil Fischer's name is associated with no less than six separate reactions. Such full descriptive names are apt to materially help and support one's memory.

The contents of the book also provide far more than might well be expected. In addition to more than 500 organic syntheses, degradations, and rearrangements, given with or without the names of authors, as well as rules and principles, *etc.* analytical procedures that are of value to the organic chemist and biochemist are also given. Examples are those associated with the names of *Liebig, Dumas, Carius, Dakin, Kjeldahl, Kuhn-Roth, Paneth, van Slyke, Tschugaeff-Zerewitinoff*, and *Zeisel*. In this area, and in technical reactions, the difficulties of setting limits to the degree of selection are obvious. Among the technological reactions included are those known by the names of *Andrussov, Bergius, Chardonnet*, and *Edeleanu*, as well as *Delbrück* and *Meisenberg*'s enzymatic production of acetone and butanol, including *Weizman*'s modification, saccharification of wood according to *Bergius, Willstätter*, and *Zechmeister* and according to *Scholler, Twitchell*'s hydrolysis of fats, and *Varrentrapp*'s cleavage of oleic acid.

For these reactions, as in all cases, the essentials of each individual reaction are discussed with exemplary brevity in formula schemes and text, and the mechanism is given, if known. Each reaction is allocated an average length of one page and is furnished with adequate references; in general, these include the first mention of the particular topic in the literature and references to recent original and review literature. The numerous cross-references between related reactions are particularly valuable.

In spite of its terseness, the text is readable and easy to follow; the layout is excellent.

The reviewer is sure that this book will meet with an excellent reception and that further editions will appear in due course. Although further reactions will presumably be added, it is to be hoped that the conciseness of the text will be preserved. The authors themselves are obviously aware that a reference work of this type, arranged according to author's names, is not intended to replace textbooks on reaction mechanisms; it nevertheless provides a useful and clear revision book and reference manual of organic reactions, including their mechanisms. The terminology introduced in this book appears to be particularly valuable; it is to be hoped that it will be widely adopted. The book deserves a place in the library of every chemist. An English edition is at present in the press.

A. Lüttringhaus [NB 978/34 IE]

Analyse der Tenside (Textband und Tafelband) – Infrarotspektroskopische und chemische Methoden (Analysis of Detergents, Infrared Spectroscopic and Chemical Methods; one volume of text and one volume of charts), by *D. Hummel*. Carl Hanser Verlag, Munich, 1962. 1st Edition. Textbook: 323 pp., 7 diagrams, 20 tables. Book of charts: 466 traces of infrared spectra, 8 correlation charts. Total price DM 156.– (about $ 40.–).

The author of this work in two volumes became known as an expert by the appearance in 1958 of his monograph on the analysis of plastics, lacquers, and gums. Through his practical work in an industrial analytical laboratory, he has acquired extensive knowledge of the application of not only physical methods, especially infrared spectroscopy, but also of chemical methods of detection and estimation. Utilizing his vast experience, he wrote the above monograph about the analysis of surface-active substances, for which he chose the term "tenside" (L. *tensus* – stretched) proposed by *E. Götte*. Building upon the fundamental work of *B. Wurzschmitt* [1] and of *Kortland* and *Dammers* [2], he has given qualitative and quantitative analytical methods for anionic, cationic, non-ionic, and amphoteric detergents, as well as for ethylene oxide adducts, including a methodical scheme of analysis based upon chemical and spectroscopic methods. A chapter of the first volume is also devoted to the identification of structural features. The volume closes with detailed tables indicating the composition of more than 250 commercial detergents, and naming methods for the detection and quantitative estimation of the various types of detergents, which are listed according to their characteristic structural features. The second volume contains the infrared spectra of diverse kinds of detergent and, further, of several fluorine derivatives, fatty acids, alcohols, phenols, hydrocarbons, and organic compounds containing nitrogen and sulfur, as well as of inorganic compounds, when these are used or are on the market as surface-active agents either by themselves or in admixture with detergents. The vast spectral data could hardly be used directly for qualitative assignments were it not clearly presented and then listed according to structural features in eight final correlation charts.

The two volumes are recommended to everyone concerned with surface-active agents or commercial products, both as an introduction to analytical studies and as a valuable work of reference. The lay-out of the monograph is very good, but unfortunately the price is relatively high.

H. Kienitz [NB 1000/40 IE]

Dictionary of Chemical Technology in Four Languages, English-German-Polish-Russian. Edited by *Z. Sobecka* with *W. Biernacki, D. Kryt*, and *T. Zadrożna*, in cooperation with *H. Stephen* and *T. Stephen*. Pergamon Press, Oxford, and Wydawnictwa Naukowo-Techniczne, Warszawa 1962. 1st Edit., 724 pp., linen £ 10.0.0.

In the main body of the dictionary, numbered entries give the equivalents of each term in all four languages, with English as the key language in the alphabetical listing. For each of the remaining three languages, there is an auxiliary index with the terms arranged alphabetically in that language, with numerical cross-references to the corresponding entry in the main part of the dictionary. It should be noted that, in the German, spellings are given starting with Z rather than with C. There is a further index, again with numerical cross-references, listing English synonyms of chemical compounds, although this is not used with full consistency: alternative names may also be found as separate listings (bromocyanogen, cyanogen bromide).

Where the same term has two or more specialized meanings, it is allotted the appropriate number of separate entries although any further definition, if given at all, is confined to an abbreviation indicating the field of use; presumably – and not unreasonably – the user is expected to ascertain the relevant entry from the context in his material. Names of compounds are often supplemented by formulae to avoid ambiguity.

About 12000 entries have been selected from almost ten times that number of listings in the card register of the Technical Terminology Division of the Polish Technical Publishing Institute. In common with all such selections, this one is bound to offend against individual tastes and interests. To the reviewer, the dictionary appeared sound on general chemistry and the classical technologies, as well as some

[1] *B. Wurzschmitt*, Z. analyt. Chem. *130*, 105 (1950).

[2] *C. Kortland* and *H. F. Dammers*, Chem. Weekbl. *49*, 341 (1953); J. Amer. Oil Chemists' Soc. *32*, 58 (1955).

technological fields of more recent growth (plastics, radiation chemistry) but somewhat deficient in disciplines such as pharmaceutical chemistry and theoretical aspects of organic chemistry and biochemistry (*e.g.* no listings are included for spasmolytics, tranquillizers, conformation, supernatant, secondary structure, or cytochemistry).

The print and layout are excellent; the use of paper in different colors for the supplementary indexes is a convenient aid to orientation.

The dictionary should be of considerable use to the reader and translator of not too specialized or theoretical texts, and as a handy first reference for the specialized translator.

J. Rudinger [NB 997/37 IE]

Ullmans Encyklopädie der technischen Chemie (Ullman's Encyclopaedia of Chemical Technology) edited by *W. Foerst*. Vols. 3–10. Verlag Urban & Schwarzenberg, Munich and Berlin 1953/58. 3rd Edit., DM 128.– (about $ 32.–) per volume. Vol. 3: 1953, XI, 851 pp., 206 figs.; Vol. 4: 1953, XI, 842 pp., 268 figs.; Vol. 5: 1954, XI, 854 pp., 237 figs.; Vol. 6: 1955, XI, 827 pp., 402 figs.; Vol. 7, 1956, XI, 848 pp. 341 figs., 4 color tables; Vol. 8, 1957, XII, 860 pp., 212 figs.; Vol. 9, 1957, XII, 812 pp., 338 figs.; Vol. 10, 1958, XII, 828 pp., 373 figs.

The articles dealing with subjects related to coal, mineral oil, and petrochemistry will be considered more closely in the following [1].

Coal (11 pp.). In this brief, lucid article, the process of coal mineralization is described, some comments are made on coal deposits, classification of coal, including notes on the structure of coal, ballast materials, and methods of investigation, and economic matters, including a table of coal and lignite production, are given. There are also numerous references to other chapters of the book which bear some relation to this subject. In the nature of things, these cross-references are the most important part of such a compact article.

Carbon (34 pp.). Here there is a good theoretical introduction (5 pp.), followed by a very good summary (17 pp.) of the use of carbon as a material for electrodes, as pure graphite, and in chemical plant construction, and lastly also a good survey on activated carbon (12 pp.). The whole chapter forms a complete unit.

Lignite (35 pp.). This exhaustive article discusses the historical development, and at greater length the formation of lignites, their chemical properties, and a comprehensive survey of existing deposits. The production is described, and a detailed treatment of the special machinery required is included. Among their uses, only briquetting is discussed. The economic survey is extensive, so that the article presents a balanced picture of all essential points with the exception of other uses.

Coal Conversion (404 pp.). This article, as is shown by the large number of pages, goes a long way towards forming a systematic presentation. The article is tightly organized and divided into 11 main sub-sections under a total of 131 headings, which are previewed in the form of an introductory table of contents, greatly simplifying searches for information. The co-ordination of the 19 authors concerned with the article is a remarkable editorial achievement. – Among the processes dealt with in detail, low-temperature carbonization of lignite coal and peat are described in 53 pages with good technical drawings and tables. This provides a satisfactory general picture and enables the various processes to be compared. – Coking of coal, treatment of crude gas, and the production of valuable coal derivatives is presented in minute detail in 105 pages. Considering that emphasis is placed upon classical and sometimes well-known processes, that extensive literature on coking exists, and that, in addition the information in this field is easier to secure, because some firms supplying coking plants provide extensive and instructive documentation, it might have been possible to save some space here. – The chapter on gasification of coal is also comprehensive (89 pp.); this is, however, justified, considering the numerous technical developments in this field. This section gives a very good and complete technical summary of all the important coal gasification processes.

This is followed by an 18-page section, the whole of which deals only with fuel gas production; this is somewhat too much space for this subject.

An article from an expert pen, which goes beyond the more narrow economics of coal conversion, deals with the hydrogenation of coal and oil. It presents a complete picture of the historical development, catalyst problems, chemical engineering developments, and modified processes, including the qualitative improvements of fuels and lubricating oils. Although these significant technical developments have meanwhile lost some of their practical importance on account of the expanding use of mineral oils compared with coal, these investigations have provided so much stimulus of general importance, that this compact presentation will still retain a permanent value.

This is then followed by smaller sections on the extraction, oxidation, and chemical after-treatment of coal.

In the manner of its overall presentation, this large chapter also constitutes a considerable contribution to chemical technology.

Fuel Gases (36 pp.). In many points, this article, which appeared considerably earlier than the contributions just mentioned, must be regarded as out-of-date. Half of it is devoted to "classical coal-gas production" with detailed descriptions of plants, although the good economical notes indicate that gasworks production represents only 11% of the entire consumption. Since this development, as mentioned in the introduction, was concluded in 1912 (!), it should now be dealt with more briefly. The history of the fuel gases, their composition and properties are also treated in too much detail. A whole page is devoted to the reduction of the gas volume to standard conditions because – it is stated – "the volume of gases depends to a great extent on pressure, temperature, and moisture content". This chapter will presumably be omitted in a later edition, and its subject matter worked into the general context.

Fuels, solid and liquid (35 pp.). This chapter, too, was very useful when the second volume of Ullmann's Encyclopaedia appeared, but it has lost much of its justification on account of later articles. Just as under the key-words coal and lignite, the formation of natural fuels is discussed, and a classification of lignites and coals is given. One third of the section is devoted to the examination of solid fuels. The section "liquid fuels" (11 pp.) is far too concise to be able to convey any of the essentialities on this subject. Two-thirds of it deals with the analysis of liquid fuels, but it is incomplete even in this respect. One page dealing with economic matters without mentioning the economics of petroleum is naturally much too scant.

Mineral Oil, Natural Gas (211 pp.). This is an extensive article, divided into 78 sub-sections, which describes the occurrence, production, purification, composition, characterization, testing, and processing of mineral oils. Half the article deals with the subject of processing. Among these sections (118 pp.), there are detailed, technically comprehensive descriptions not only of distillation and cracking, but also of special processes for manufacturing high-grade propellants and of refining operations for lubricants and fuel oils. Extensive references are given to the patent literature of special processes like polymerization, alkylation, isomerization, refining, paraffin removal, etc. All the problems of processing mineral oil and its derivatives in this chapter are confined to fuel and lubricating oils. The section on natural gas (24 pp.) records physical data in great detail (some condensation might perhaps have been possible here); the uses are dealt with in half a page, largely by way of references. In the following relatively short economic section, too, there is unfortunately no further mention of natural gas. In the section on the uses of natural gas, comparison of the several possible uses with quantitative data, *i.e.* the consumption for individual uses, *etc.*, would have been desirable. The chapter on mineral oil and natural gas contains an addendum of a

[1] Cf. Angew. Chem. *72*, 283 (1960); *73*, 662 (1961).

single page about mineral oil and natural gas as a raw material for the chemical industry with many references to other chapters of this work. Although it is right not to deal with the many branches of petrochemical processes in the chapter on the uses of mineral oil, but rather under the products resulting therefrom, it would nevertheless have been very desirable to have here a more detailed survey with flow sheets and quantitative data. – On the whole, the chapter on mineral oils and natural gas forms a good section complete in itself. Even a person not working in the petroleum industry will find it a very handy guide.

Hydrocarbons (181 pp.). After a very good theoretical introduction of 18 pages, more than half of the section is devoted to a description of the chemical and in particular the physical properties of hydrocarbons. A sub-section (41 pp.) deals with transformations of hydrocarbons, and another sub-section (32 pp.) with the separation of hydrocarbons. The entire chapter contains technologically widely differing materials. In the description of the hydrocarbons, the characteristics of technically important raw materials are included, and so are the classification of fused polycyclic hydrocarbons and their nomenclature. In this chapter, the toxicological appendices attached to the individual hydrocarbons are very good and useful. The essential and basic processes of petrochemistry are described among the hydrocarbon transformations, and here there is a good and detailed presentation in particular of the petrochemical production of acetylene, ethylene, and other olefins. (The production of butadiene has already been dealt with in the previous section in connection with the characterization of butadiene). The fact that a good and very detailed article is entirely devoted to the subject of hydrocarbon separation is very welcome, because the problems of petrochemical separation are particularly important in chemical engineering. On reading this chapter, an overall impression is gained of the rapid flow of development of the subject under discussion.

Bitumen (35 pp.). This chapter is both clear and detailed. Half of it deals with asphalt, the other half with fossil waxes. Natural asphalt is described in detail by comparison with asphalt derived from mineral oil. With regard to the manufacture of roofing felt, which is presented here with a picture, a cross-reference to the entry "Dachpappe" (roofing felt) would have been sufficient. The section on "fossil wax", which also mentions general aspects of wax chemistry (including Fischer-Tropsch waxes, but excluding montan waxes), suffers a little from the fact that the chemistry of waxes is only dealt with in detail under the entry "Wachse" (waxes).

Hydrogenation of Carbon Monoxide (63 pp.). This chapter, (from which the syntheses of methanol have been excluded) gives a comprehensive account of an extensive technical development which had its origin in the work of *Franz Fischer*. Eleven authors, most of whom number among the pioneers of this development, have joined together for this composite account. Although this process may have lost much of its economic importance because of the advances made by mineral oil, a detailed picture of this kind is nevertheless justified, because a large amount of chemical engineering knowledge of permanent value was gathered in the course of this work. There are few processes in which chemical engineering potentialities have been developed so completely for purposes of comparison: *viz.* work on solid bed, fluidised bed, and dust catalyst reactors, at low, medium, and high pressures, in the gas and the liquid phase, and with different methods of heat removal. With the forced development that took place during the second world war, and with the official comparisons as a base, this process provides a rare wealth of material for technological comparisons and computational investigations. Within the framework of this general treatment, the iron-catalysed large scale synthesis (Eisenkontakt-Hochlastsynthese) developed by Ruhrchemie-Lurgi after the war and embodied technically at Sasolburg in Africa is dismissed rather briefly. Because of the numerous other working methods in connection with this process, which are all given in full, the reader who is less at home in this subject matter may occasionally have difficulties in deciding when the work described still belongs to the experimental stage or when it deals with technically important syntheses. Despite these minor limitations, the article in general must be regarded as very successful.

Rubber (119 pp.). This article comprises well-balanced joint contributions of eight authors from Leverkusen. Despite its scope, the article is very compact, offers many details, and is at present probably the most comprehensive description of its kind dealing with rubber technology. Besides the production of natural rubber and the description of the various rubber syntheses, much space is devoted to rubber processing and to rubber compounding materials. Butyl rubber and Hypalon might have been dealt with at greater length. The ICI and DuPont polyurethanes, too, are only dealt with very briefly. (There is a misprint on p. 383: instead of *W-Schule* it ought to be *W. Scheele*).

Although the well-known static test methods are admittedly described in the chapter on technical examination, there are no more than six lines – apart from a description of the DeMattia test – on the increasingly important dynamic tests in the section on "the determination of damping" (p. 412). On the other hand, the description of the falling ball impact test might have been omitted, because this test is based on rather dubious starting data.

On looking over the material on the subjects "mineral oil, coal, petrochemistry" (here used in a very wide sense), which together with the entries just discussed, comprises a total of 1174 pages, the most conspicuous fact is the extraordinarily rapid current technical development in this field. Starting with the old, traditional working methods, we have here a more or less complete revolution in the raw material supply of the larger part of chemistry. A crucial date for this change in Germany was February 1st, 1953: from this time onwards, mineral oil products became available for new, large-scale technical processes. This led to considerable acceleration of what had already been a lively development, and there will be further lasting shifts to follow. In view of these events, it will be found that the picture of these subjects presented by *Ullmann* is very successful. Such circumstances also reveal the importance of a good index, since even with the best will in the world it is not always possible to arrange such a torrent of events by preparatory planning and design of such a work. Here, too, the advantages of an alphabetic arrangement become apparent, for this permits further additions in subsequent entries (*e.g.* petrochemistry, coal, synthesis gas). On the whole, it may be said that the subjects coal, mineral oil, and petrochemistry have been presented in a very good, up-to-date, and lively manner.

Here the reviewer wishes to express his sincere thanks to all the colleagues who assisted him by helpful discussions in evaluating individual articles. *H. Sachsse* [NB 989/36 IE]

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The Mössbauer Effect and its Significance in Chemistry

BY DOZENT DR. E. FLUCK, DR. W. KERLER, AND W. NEUWIRTH

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DER UNIVERSITÄT HEIDELBERG (GERMANY)

Resonance fluorescence of recoil-free γ-rays from atomic nuclei depends on the state of the chemical bonding of the atoms. The latter influences the position of the energy level of the atomic nuclei, so that the energy required for excitation of resonance fluorescence is somewhat smaller or greater than the energy of the γ-quanta emitted by the radiation source. In order to obtain resonance fluorescence, therefore, the radiation source and absorber have to be kept moving relative to each other. If the intensity of the resonance fluorescence is plotted against this relative velocity, Mössbauer spectra are obtained. The positions of the lines in these spectra make it possible to draw conclusions about the nature of the atom's bonds. The efficiency of this method is demonstrated by illustration with numerous iron compounds. It was shown, for instance, that the iron atoms in "insoluble Prussian Blue" have well-defined oxidation levels. "Turnbull's Blue" shows the identical spectrum. A structure could be ascribed to tri-iron dodecacarbonyl that also explains the diamagnetism of the compound.

Introduction

It was long believed that the physical behaviour of the atomic nucleus was independent of the state of chemical bonding of the atom. However, this is not so. *Knight* found in 1949 that the conditions for nuclear magnetic resonance of phosphorus depend on the state of bonding of the phosphorus atom [1]. It was found later that the same phenomenon occurs with other isotopes. Similarly, with the Mössbauer effect, another resonance phenomenon in atomic nuclei, the state of chemical bonding of the atom is of importance.

I. The Mössbauer Effect

The effect discovered by *R. L. Mössbauer* [2–4] concerns the resonance fluorescence of so-called recoil-free γ-radiation from atomic nuclei.

Fluorescence phenomena have been known for a long time. By absorption of a light quantum hν of sufficient energy an atom or a molecule can be excited, *i.e.* raised to a higher quantum level (an electron is lifted into a higher shell). On the return of the atom or molecule from the excited level to its ground state, the energy it had absorbed is re-emitted in the form of light quanta. If the atom or molecule returns to the ground state *via* selectively either one or more than one quantum levels, the energy of the emitted light quanta is smaller than that of the absorbed light quanta. If the atom or molecule has been lifted by the absorbed light quantum only just to the first excited level, however, only such light quanta can be emitted on its return to the ground state as have uniform energy identical with that of the absorbed light quanta. This special case of fluorescence is called resonance fluorescence.

A set-up for observing resonance fluorescence is shown diagrammatically in Figure 1. It consists of a radiation source Q, the absorber A, and the detectors I and II, which serve to determine the intensity of the radiation. One detector is placed in the radiation beam, the second is placed perpendicularly to it. Unless the energy of the light quanta emitted by the radiation source corresponds to the energy of the first excited state of the electron shell of absorber A, no resonance fluorescence occurs, in accordance with the above explanations. Detector I will then indicate the full intensity passing

[1] *W. D. Knight*, Physic. Rev. *76*, 1259 (1949).
[2] *R. L. Mößbauer*, Z. Physik *151*, 124 (1958).
[3] *R. L. Mößbauer*, Naturwissenschaften *45*, 538 (1958).
[4] *R. L. Mößbauer*, Z. Naturforsch. *14a*, 211 (1959).

from the radiation source into the solid angle of the detector, while detector II will not indicate any radiation whatever (Fig. 1 a). If, however, the energy of the light quanta emitted by Q corresponds exactly to the excitation energy of the

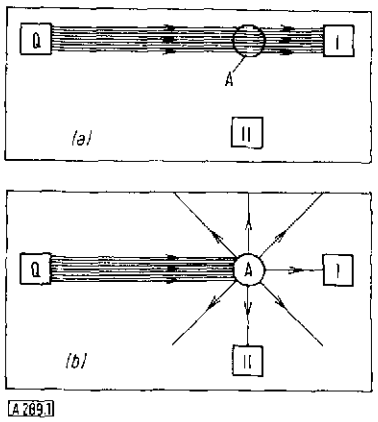

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Fig. 1. Diagrammatic representation of resonance fluorescence.
(a) no resonance, (b) resonance.
Q = radiation source, A = absorber, I and II = radiation detectors

electron shell, resonance occurs. Isotropic radiation is emitted by the absorber and can be measured by means of detector II (Fig. 1 b). In practice, the occurrence of resonance is recognized by the fact that the intensity of the radiation registered by detector I (transmission) decreases, while detector II indicates the reception of some radiation (scattering). The radiation source Q, which supplies the light quanta of such well-defined energy that are necessary for resonance fluorescence, consists of atoms of the same kind as those of the absorber. The atoms in the radiation source, however, are already excited and emit light quanta of the correct energy on passing back into the ground state.

γ-Radiation emitted by excited atomic nuclei, like the light originating from the electron shells, is electromagnetic radiation, so that, here again, resonance fluorescence should be observable. Generally, however, because of their considerably higher energy, γ-quanta impart a measurable recoil to the nucleus during emission, so that part of the excitation energy of the nucleus is lost as recoil energy. Hence any γ-quantum emitted has insufficient energy to excite a nucleus of the absorber. An analogous loss by recoil occurs during absorption. These losses by recoil can be compensated by imparting a velocity to the nucleus during emission of the γ-quantum; this velocity is in the direction of the absorber and corresponds exactly to the loss of energy expected. This effect can be achieved, for example, by moving the radiation source in a centrifuge or by heating it (increase in thermal velocity). The resulting Doppler shift ensures that the quantum has again the energy necessary for excitation.

The effects obtained in this way are very small, however, as only a minute percentage of the atoms will have just the right velocity. This difficulty is even more pronounced because the relative widths of the lines are usually much less than those of lines in optical spectra. The energy of light quanta emitted by the radiation source in optical resonance fluorescence with small quantum energy losses frequently lies within the width of the lines, *i.e.* it is still sufficient to excite the electrons of the absorber atom. In contrast, the relative widths of γ-lines of atomic nuclei are much smaller. The line width is a consequence of Heisenberg's uncertainty principle. The product of the uncertainty of energy and the uncertainty of time has the value of Planck's efficiency quantum, *i.e.* the product of the line width and the mean life of the excited state must be equal to the efficiency quantum. If the line widths are determined, the mean life of the excited states can be evaluated.

In the arrangement according to Mössbauer, the loss resulting from recoil is not compensated, but avoided altogether. If the radiating atom is solidly built into a crystal lattice, the crystal absorbs the recoil momentum, and there is virtually no loss of energy, unless vibrations are started in the lattice during emission. The condition for resonance is therefore fulfilled for these recoil-free quanta without further ado, and experiments can be carried out in a manner analogous to the measurement of resonance fluorescence shown diagrammatically in Fig. 1 b. The resonance can be stopped by imparting a velocity to the radiation source, relative to the absorber, this velocity being connected with a change in energy of the γ-quanta by the Doppler effect.

If the resonance is observed by absorption, *i.e.* followed by means of detector I in Figure 1 b, the intensity distribution shown in Figure 2 results as a function of the

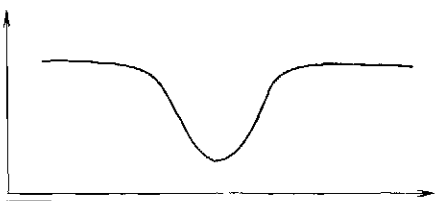
A 289.2

Fig. 2. Change in the intensity of radiation due to the Mössbauer effect.
Ordinate: Intensity of radiation received by detector I (transmission).
Abscissa: Velocity of the radiation source relative to the absorber.

velocity of the absorber relative to the radiation source. If, for some reason, the first energy level of the atomic nuclei of the absorber is shifted upwards or downwards, so that the energy required for excitation is somewhat smaller or greater than that of the γ-quanta emitted by the radiation source, the radiation source and absorber have to be moved relative to each other. The velocities involved are very small, since the change in energy has to be only of the order of the width of the lines, and this, as mentioned above, is very small for γ-lines of atomic nuclei.

Since not all the radiating atoms built into a crystal lattice emit γ-quanta "without recoil", but vibrations are started in the lattice to some extent, thereby causing loss of energy from the quanta, the magnitude of the Mössbauer effect depends on the proportion of recoil-free quanta in terms of the total intensity, *i.e.* the Debye-Waller factor. The effect is greater, the less the probability of excitation of vibrations in the lattice, *i.e.* the smaller the quantum energy, the lower the temperature of the crystal, and the more rigid the atomic bonding in the lattice.

Mössbauer originally discovered the effect with ^{191}Ir nuclei, which have a γ-quantum energy of 129 keV; ^{191}Os was used as radiation source. The latter decays according to the diagram shown in Figure 3 with a half-life of 16 days and emission of β-rays to give the second

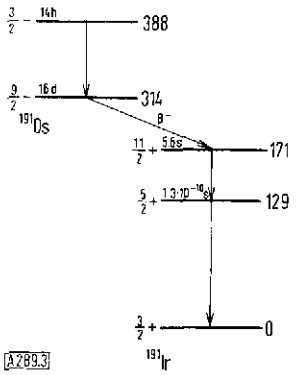

Fig. 3. Radioactive decay scheme for ^{191}Os → ^{191}Ir.

excited state of ^{191}Ir. After loss of a γ-quantum of 42 keV, the first excited state is obtained. The ground state is reached by emission of 129 keV γ-quanta. Iridium nuclei of the absorber present in the ground state are excited by these γ-quanta and return to the basic state with emission of fluorescent rays.

In order to measure the line width of 4.7×10^{-6} eV, the absorber had to be moved with a velocity of a few cm/sec relative to the radiation source. The line width yields a value of about 10^{-10} sec for the mean life of the first excited state of ^{191}Ir nuclei.

A considerably lower line width was obtained for ^{57}Fe nuclei. Excited ^{57}Fe nuclei are formed on decay of ^{57}Co (cf. Fig. 4). Their quantum energy is 14.4 keV, the

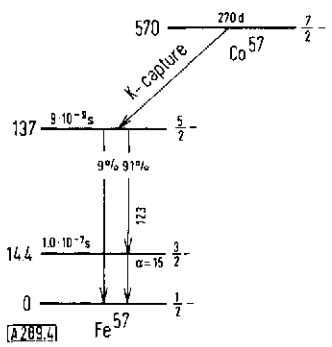

Fig. 4. Radioactive decay scheme for ^{57}Co → ^{57}Fe.

lifetime of the first excited state is 1.0×10^{-7} sec, and the resulting line width is 4.8×10^{-9} eV. The velocities required for measurement of its line width are of the order of about 0.1 mm/sec. A velocity of 0.1 mm/sec corresponds to an energy of 4.8×10^{-9} eV.

On the basis of these data, ^{57}Fe proves to be very suitable for studying effects that are conditioned by the nature of the chemical bond.

In principle, such studies are possible with all nuclei having a low energy for the first excited state, a sufficiently small line width, and a sufficiently small conversion coefficient. The conversion coefficient gives an indication of the relative proportion of conversion electrons and γ-quanta emitted when the nucleus returns to the ground state. Instead of emitting a γ-quantum, a nucleus is also capable of passing back into the ground state when an electron of the inner orbit absorbs the excitation energy and leaves the atomic shell. This type of conversion is considerable, especially with small γ-quanta. The conversion coefficient for ^{57}Fe at the 14.4 keV level is about 15. Finally, the nuclear spin should not exceed 3/2, since otherwise the structure of the spectrum becomes very complex and is difficult to analyse. If known isotopes are considered from this point of view, ^{119}Sn proves very suitable, too, in addition to ^{57}Fe. However, nuclei like ^{61}Ni, ^{67}Zn, ^{161}Dy, ^{169}Tm, and ^{197}Au are also usable.

II. Applications of the Mössbauer Effect

1. Physical Applications

The Mössbauer effect can be used to determine the lifetime of energy states from the line width of resonance and to measure resonances as a function of various influences. With the aid of the narrow lines of ^{57}Fe (ratio of line width to quantum energy about $1:10^{12}$), it was possible to prove the energy shift of γ-quanta in the gravitational field, *i.e.* to ascertain that γ-quanta had changed their energy content in the gravitational field of the earth, after travelling a certain distance [5].

Furthermore, the Zeeman effect, as known from the electron shell, *i.e.* the splitting of excited states in a magnetic field, which is very small for nuclei on account of their small magnetic moments, could only be measured directly with the aid of the Mössbauer effect [6]. Thus, the resonance line of ^{57}Fe is split into six components. The very strong magnetic field required near the nucleus to effect the splitting is produced by the crystal field and the electrons. The extent of the splitting of the lines yields the magnetic nuclear moments or the field around the nucleus.

2. Chemical Applications

Potential applications of the Mössbauer effect in chemistry arise from the observation that the position and structure of the resonance lines depend on the state of the chemical bonding of the atom. Owing to the particularly favorable properties of the isotope ^{57}Fe, the phenomena of the isomeric shift, the electric quadrupole interaction effect [7], and the temperature shift [8] described in the subsequent sections were first measured in detail using this isotope. Details of the measurements and conclusions drawn from the data have been given elsewhere [9, 10].

a) Apparatus

Figure 5 shows the principle of the apparatus. The substances under examination served as resonance absorbers. Their absorption was measured as a function of the relative velocity between absorber and source. γ-Quanta emitted by the radiation source can penetrate

[5] *R. V. Pound* and *G. A. Rebka jr.*, Physic. Rev. Letters *4*, 337 (1960).

[6] *S. S. Hanna, J. Heberle, C. Littlejohn, G. J. Perlow, R. S. Preston*, and *D. H. Vincent*, Physic. Rev. Letters *4*, 177 (1960).

[7] *O. C. Kistner* and *A. W. Sunyar*, Physic. Rev. Letters *4*, 412 (1960).

[8] *R. V. Pound* and *G. A. Rebka, Jr.*, Physic. Rev. Letters *4*, 274 (1960); *B. D. Josephson, ibid. 4*, 341 (1960).

[9] *W. Kerler, W. Neuwirth*, and *E. Fluck*, Z. Physik, in the press.

[10] *W. Kerler, W. Neuwirth, E. Fluck, P. Kuhn*, and *B. Zimmermann*, Z. Physik *173*, 321 (1963).

through the resonance absorber, *i.e.* the substance under examination, reach a NaI crystal, and be registered by a photomultiplier. In order to move the radiation source

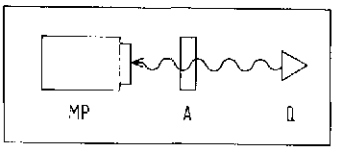

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Fig. 5. Diagrammatic view of apparatus for measuring the Mössbauer effect.
MP = photomultiplier, A = absorber, Q = radiation source.

relative to the absorber, it can be connected, for example, rigidly with the voice coil of a loudspeaker. A somewhat more complicated arrangement described by *Kerler* and *Neuwirth* [11] was used for the measurements on account of the accuracy desired.

The sample is pressed into plexiglass frames of 11 mm internal diameter, 20 mm external diameter, and 0.5–1.0 mm thickness and sealed with cellulose tape on both sides. Similar frames, made from aluminum foil 30 μ thick, are used for investigating liquids. The liquid is filled in through a narrow slit in the frame, and this is sealed with a cement. The absorber should contain 4–30 mg of Fe per cm^2. Metallic absorbers are prepared with a thickness of 10–30 μ. The absorber is placed in a thermally insulated, air-tight chamber that can be heated or cooled by thermal conduction. The temperature of the chamber is measured with a thermocouple.

As *Barloutaud* [12] has shown, scattered radiation can be measured, too. These measurements also make it possible to examine thick objects.

b) Radiation Source

In order to study the resonance of ^{57}Fe nuclei, ^{57}Co atoms were built into a crystal lattice to serve as radiation source. ^{57}Co atoms decay according to the series shown in Figure 4. Several authors use sources in which ^{57}Co has been allowed to diffuse into stainless steel, although then the resulting line width is about twice the normal one. Approximately the same line width is obtained with ^{57}Co in copper. A particularly narrow emission line results if platinum is used instead of stainless steel; intense absorption of radiation in the electron shell of platinum can be largely avoided by allowing the ^{57}Co to diffuse into the surface layers only. The emission line of a ^{57}Co source in palladium is similarly narrow as that in platinum and, at the most, 10 % wider than the natural line width. Moreover, absorption of γ-radiation by palladium is less than by platinum.

The line shifts obtained with ^{57}Co in palladium are 0.165 ± 0.002 mm/sec higher than the values determined with ^{57}Co in platinum; the values obtained with ^{57}Co in stainless steel (55 % Fe, 25 % Cr, 20 % Ni) are 0.432 ± 0.002 mm/sec higher than those determined with ^{57}Co in platinum.

Unless otherwise indicated, all the shifts reported in this paper refer to ^{57}Co in platinum at 25 °C as radiation source.

[11] *W. Kerler* and *W. Neuwirth*, Z. Physik *167*, 176 (1962).

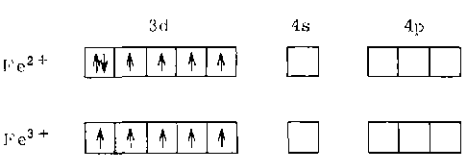
[12] *R. Barloutaud, J. L. Picou*, and *C. Tzara*, C. R. hebd. Séances Acad. Sci. *250*, 2705 (1960).

c) Isomeric Shift

The influence of the state of chemical bonding of the iron atom is obtained from the magnitude of the isomeric shift δ and the quadrupole interaction described in Section 2d.

If the γ-radiation emitted by the radiation source strikes an absorber, the atoms of which are present in the same chemical compound and in the same crystal lattice as is present in the source, resonance occurs. This is no longer so, however, if the atoms in the absorber exist in a state of chemical combination different from that of the atoms of the radiation source. In order to fulfil the condition for resonance, it is necessary then, as a rule, to move the absorber relative to the radiation source and thus to change the energy of the quanta received in such a way that they correspond to the excitation energy of the nuclei in the absorber substance. The absorber must be moved either towards the radiation source or away from it, depending on whether the excitation energy of the absorber nuclei is greater or smaller than the energy of the γ-quanta emitted by the radiation source. These shifts are expressed in mm/sec relative to the zero velocity of an arbitrary radiation source and are termed line shifts. Each line shift is made up of an isomeric shift and a temperature shift.

The isomeric shift is a linear function of the s-electron density around the nucleus and is caused by the interaction of the s-electrons with the nucleus, the latter's charge being distributed in different ways in the excited and ground states, respectively. The isomeric shift decreases with increasing s-electron density around the nucleus, *i.e.* any increase in the s-electron density causes a shift of the resonance line toward negative velocity values. In the case of the ^{57}Fe isotope, the magnitude of the isomeric shift is largely determined by the occupation of the 3d and 4s orbitals and any external influences upon these (*e.g.* covalent bond character or fields from neighboring ions). This means, for example, that the shift of Fe^{2+} ions is larger than that of Fe^{3+} ions, since the 3s electrons are screened to a greater extent by the additional 3d electron in the former [13, 14].



The high s-electron density in metallic iron which originates from the partial occupation of the 4s orbit causes a pronounced shift towards negative values.

Table 1 shows that the isomeric shifts have characteristic values for different groups of iron compounds. The shifts at about 120 °C for Fe^{2+} salts fall within a range from 0.9 to 1.0 mm/sec, those for Fe^{3+} salts within a range from 0.0 to 0.1 mm/sec, while complex com-

[13] *S. De Benedetti, G. Lang*, and *R. Ingalls*, Physic. Rev. Letters *6*, 60 (1961).

[14] *L. R. Walker, G. K. Wertheim*, and *V. Jaccarino*, Physic. Rev. Letters *6*, 98 (1961).

Table 1. δ-Shifts and quadrupole splittings for iron and iron compounds. Radiation source: ^{57}Co in platinum

Element or compound	Temp. [°C]	Shift [mm/sec]	Quadrupole splitting [mm/sec]
$FeSO_4 \cdot 7H_2O$	−107	+0.994 ± 0.005	3.470 ± 0.010
	+ 25	+0.917 ± 0.005	3.192 ± 0.010
$Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$	+ 25	+0.896 ± 0.004	1.725 ± 0.004
$FeCl_2 \cdot 4H_2O$	−115	+0.945 ± 0.005	3.090 ± 0.010
	+ 25	+0.878 ± 0.005	3.000 ± 0.010
$Fe(COO)_2 \cdot 2H_2O$	−107	+0.920 ± 0.007	1.942 ± 0.010
	+ 25	+0.855 ± 0.007	1.729 ± 0.010
$Fe_3(PO_4)_2 \cdot 8H_2O$	+ 25	+0.90 ± 0.08	2.86 ± 0.11
FeF_2 [15]	+ 25	+0.93 ± 0.05	2.68 ± 0.05
$Fe[SiF_6] \cdot 6H_2O$ [16]	−183	+1.13 ± 0.04	3.70 ± 0.04
$FePO_4 \cdot 4H_2O$	−110	+0.146 ± 0.006	0.657 ± 0.007
	+ 25	+0.080 ± 0.006	0.625 ± 0.007
$FePO_4$, calcined	−109	+0.009 ± 0.005	0.616 ± 0.007
	+ 25	+0.060 ± 0.005	0.620±0.007
Ferric oxide·xH_2O	+ 25	+0.013 ± 0.012	0.62 ± 0.03
Fe_2O_3 [17]	+ 25	0.00 ± 0.03	0.24 ± 0.03
$Fe(NO_3)_3 \cdot 9H_2O$	−104	+0.09 ± 0.03	0.6
	+ 25	+0.04 ± 0.03	0.6
$NH_4Fe(SO_4)_2 \cdot 12H_2O$	−108	+0.1 ± 0.1	0.6
	+ 25	+0.1 ± 0.1	0.6
$Fe_2(SO_4)_3 \cdot xH_2O$	+ 25	+0.101 ± 0.006	0.282 ± 0.010
$FeCl_3 \cdot 6H_2O$	+ 25	+0.555 ± 0.008	
$K_4[Fe(CN)_6] \cdot 3H_2O$	−105	−0.344 ± 0.005	
	+ 25	−0.394 ± 0.005	
$(NH_4)_4[Fe(CN)_6]$	−128	−0.361 ± 0.003	
	+ 25	−0.404 ± 0.003	
$Cu_2[Fe(CN)_6]$	−125	−0.391 ± 0.005	
	+ 25	−0.445 ± 0.006	
$Ag_4[Fe(CN)_6]$	−104	−0.409 ± 0.006	
	+ 25	−0.469 ± 0.006	
"Soluble Prussian Blue"	−127	(I) −0.460 ± 0.008	
$KFe[Fe(CN)_6]$		(II) +0.103 ± 0.027	0.40 ± 0.04
	+ 25	(I) −0.359 ± 0.013	
		(II) −0.12 ± 0.06	0.43 ± 0.09
Prussian Blue	−121	(I) −0.475 ± 0.008	
$Fe_4[Fe(CN)_6]_3$		(II) +0.137 ± 0.008	0.604 ± 0.012
	+ 25	(I) −0.514 ± 0.008	
		(II) +0.046 ± 0.008	0.570 ± 0.012
Turnbull's Blue	−129	(I) −0.463 ± 0.009	
$Fe_4[Fe(CN)_6]_3$		(II) +0.125 ± 0.009	0.573 ± 0.009
	+ 25	(I) −0.505 ± 0.006	
		(II) +0.056 ± 0.006	0.500 ± 0.009
$K_3[Fe(CN)_6]$	−106	−0.422 ± 0.003	0.358 ± 0.003
	+ 25	−0.471 ± 0.003	0.280 ± 0.003
$Cu_3[Fe(CN)_6]_2$	−127	−0.455 ± 0.007	0.755 ± 0.003
	+ 25	−0.507 ± 0.007	0.483 ± 0.005
$Ag_3[Fe(CN)_6]$	−126	−0.441 ± 0.006	0.858 ± 0.005
	+ 25	−0.494 ± 0.008	0.767 ± 0.008
$Na_2[Fe(CN)_5NO] \cdot 2H_2O$	−107	−0.567 ± 0.003	1.725 ± 0.006
	+ 25	−0.607 ± 0.003	1.712 ± 0.006
$Na_3[Fe(CN)_5NH_3] \cdot H_2O$	−127	−0.285 ± 0.006	0.663 ± 0.006
	+ 25	−0.340 ± 0.006	0.671 ± 0.004
$Na_4[Fe(CN)_5NO_2]$	−127	−0.284 ± 0.007	0.855 ± 0.005
	+ 25	−0.342 ± 0.007	0.854 ± 0.005
$Na_5[Fe(CN)_5SO_3]$	−123	−0.321 ± 0.005	0.718 ± 0.005
	+ 25	−0.378 ± 0.005	0.724 ± 0.005
$Fe(CO)_5$	−133	−0.447 ± 0.008	2.530 ± 0.008
	− 46	−0.466 ± 0.006	2.505 ± 0.006
$Fe(CO)_5$ in solution	−126	−0.426 ± 0.012	2.562 ± 0.016
	− 72	−0.442 ± 0.016	2.575 ± 0.012
$Fe(CO)_4I_2$	−126	+0.09 ± 0.03	0.74 ± 0.03
$Fe_2(CO)_9$	−120	−0.195 ± 0.007	0.400 ± 0.009
	+ 25	−0.275 ± 0.007	0.365 ± 0.009
$Fe_3(CO)_{12}$	−126	(I) −0.251 ± 0.006	1.093 ± 0.006
		(II) −0.304 ± 0.005	
$Fe_3(CO)_{12}$	− 85	(I) −0.281 ± 0.006	1.052 ± 0.006
		(II) −0.327 ± 0.007	
K_2FeO_4	−128	−1.203 ± 0.006	
	+ 25	−1.262 ± 0.006	
$BaFeO_4 \cdot H_2O$	−132	−1.200 ± 0.008	
	+ 25	−1.258 ± 0.008	
$BaFeO_4$, anhydr.	−120	−1.162 ± 0.012	
	+ 25	−1.213 ± 0.012	
FeS_2 (pyrites)	−136	+0.034 ± 0.003	0.635 ± 0.003
	+ 25	−0.032 ± 0.003	0.627 ± 0.003
FeS_2 (marcasite)	−129	0.000 ± 0.006	0.531 ± 0.005
	+ 25	−0.072 ± 0.006	0.523 ± 0.005
$[Fe(dipyridyl)_3]Cl_2$	−128	+0.037 ± 0.002	0.345 ± 0.003
	+ 25	−0.013 ± 0.003	0.340 ± 0.005
$K_3[Fe(oxalato)_3]$	−128	+0.032 ± 0.024	
	+ 25	−0.008 ± 0.024	
Haemin hydrochloride	−123	−0.350 ± 0.016	
	− 42	−0.373 ± 0.016	
Black Roussin's salt	−123	−0.222 ± 0.004	0.895 ± 0.005
$K[Fe_4S_3(NO)_7]$	+ 25	−0.280 ± 0.005	0.872 ± 0.010
Red Roussin's salt	−125	−0.275 ± 0.005	0.665 ± 0.004
$K_2[Fe_2S_2(NO)_2]$	+ 25	−0.335 ± 0.006	0.621 ± 0.005
Fe	−110	−0.273 ± 0.006	
	+ 25	−0.348 ± 0.006	
Vacromium (a stainless steel, 55 % Fe, 25 % Cr, 20 % Ni)	−112	−0.354 ± 0.007	
	+ 25	−0.425 ± 0.007	
$KFeS_2$	−145	−0.091 ± 0.008	0.450 ± 0.020
	+ 25	−0.176 ± 0.005	0.501 ± 0.005
$KFeO_2$	−123	−0.12 ± 0.04	0.09 ± 0.02
	+ 25	−0.19 ± 0.04	0.08 ± 0.02

[15] *G. K. Wertheim*, Physic. Rev. *121*, 63 (1961).

[16] *C. E. Johnson, W. Marshall*, and *G. J. Perlow*, Physic. Rev. *126*, 1503 (1962).

[17] *G. Burns*, Physic. Rev. *123*, 1634 (1961).

pounds of iron show shifts between −0.6 and +0.1 mm/sec. At δ ≈ −0.27 mm/sec, the shift for metallic iron falls into this last range.

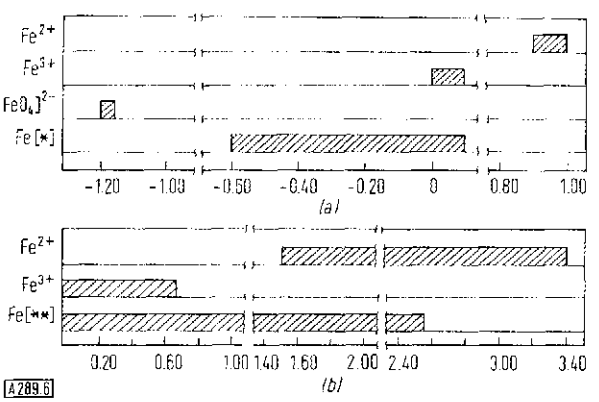


Fig. 6. (a) Values for the isomeric shifts and (b) values for the quadrupole splittings of Mössbauer lines in ferrous and ferric compounds.
Radiation source: ^{57}Co in platinum at 25 °C.
Abscissa: Velocity of the source relative to the absorber [mm/sec].
Fe [*] = iron in complexes and metals.
Fe [**] = iron in complexes.

The shifts are influenced by temperature. The proportion of a temperature shift is generally small in relation to the differences in isomeric shift and is of the order of 0.1 mm/sec. Between −120 and +80 °C, the temperature function is virtually linear (Fig. 7).

The temperature shift, like the magnitude of the Debye-Waller factor, reflects the properties of the vibrational spectrum. The temperature shift is proportional to the internal energy of the crystal, which reaches a saturation value on excitation of all lattice vibrations. The gradient $-d\delta/dT$ is due solely to the temperature shift on the assumption that the s-electron density is independent of temperature. Whether this

is actually true is a moot point. In principle, variation of the s-electron density with temperature seems possible if strong fields which vary with temperature are present.

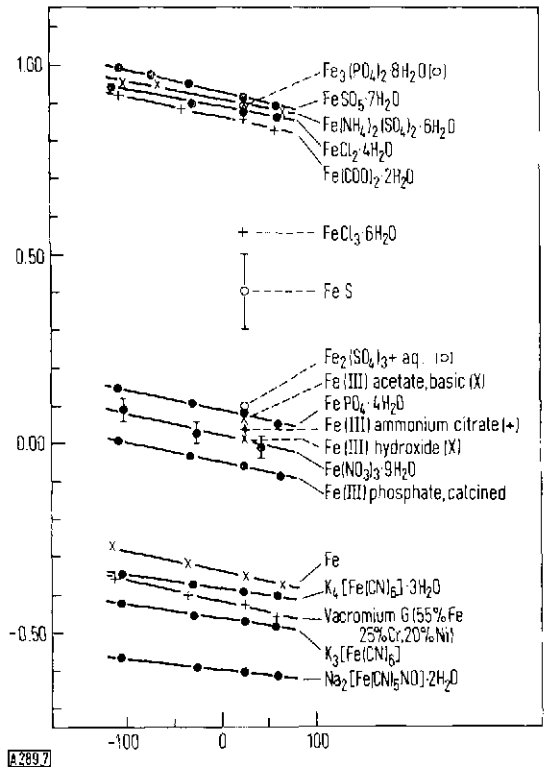


Fig. 7. δ-Shifts as a function of temperature.
Ordinate: δ [mm/sec].
Abscissa: temperature [°C].

d) Quadrupole Splitting

It is often found that the resonant rays emitted by the substance under examination do not consist of one but two lines, even if all the atoms of the absorber are in the same state of chemical bonding.

This quadrupole splitting of the resonance line arises from interaction of the electric field gradient around the nucleus with the electric quadrupole moment of the excited ^{57}Fe nucleus. The field gradient around the nucleus depends on the electronic configuration of the nucleus and on its environment. Conclusions can therefore be drawn from the quadrupole splitting about the nature of the chemical bonding and of the crystal lattice.

The quadrupole splittings ε (distances between the two lines) of the compounds examined are shown in Table 1 and Figure 6b. In Figure 8, ε for some compounds is represented as a function of temperature.

Fe^{3+} salts show only minor splittings, *viz.* up to about 0.6 mm/sec [11] (Fig. 9a). These are caused solely by the field gradients produced by the crystal lattice around the nucleus, since the free Fe^{3+} ion possesses a spherically symmetrical charge distribution and does not give rise to interaction with the electrical quadrupole moment. The field gradients in the crystal are intensified further, by a factor of about 7, by Sternheimer anti-shielding of the Fe^{3+} shell, a polarization effect. The relatively low influence of temperature on quadrupole splitting seems

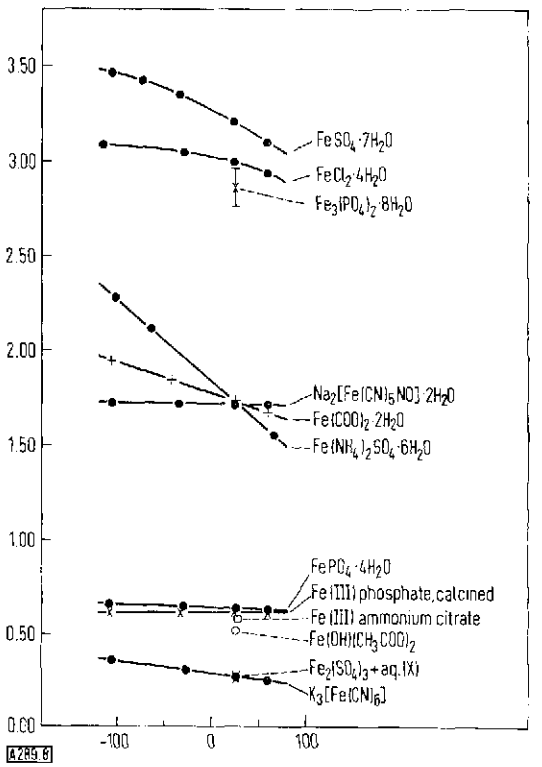


Fig. 8. Quadrupole splittings ε of absorption lines as a function of temperature.
Ordinate: ε [mm/sec]
Abscissa: temperature [°C]

to be caused in the case of the Fe^{3+} salts, according to an interpretation given by *Burns* [17], by different homogeneous contraction of the crystal in two axial directions.

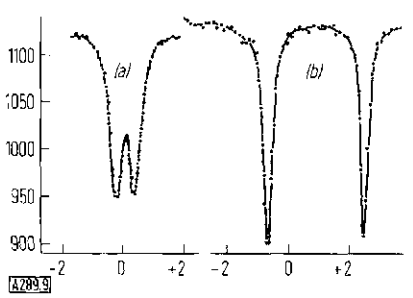


Fig. 9. Mössbauer spectra (a) of $FePO_4 \cdot 4\,H_2O$ and (b) of $FeSO_4 \cdot 7\,H_2O$
Ordinate: transmission [arbitrary units]
Abscissa: velocity of the source relative to the absorber [mm/sec]

The Fe^{2+} salts show very marked quadrupole splitting (Fig. 9b), which is caused by the additional d-electron [13]. Depending on the temperature, this electron occupies energy levels split in the crystal field; this results in a relatively steep field gradient, markedly dependent on temperature, around the nucleus.

In the octahedral complex compounds of iron, two of the 3d-orbitals of the iron ion are used for the formation of the six hybrid orbitals, and the 3d-electrons therefore occupy the remaining three 3d-orbitals. These are fully occupied in the case of a complex like $[Fe(CN)_6]^{4-}$, and this leads to a spherically symmetrical charge distribution. Accordingly, potassium ferrocyanide $K_4[Fe(CN)_6] \cdot 3\,H_2O$ does not show any quadrupole splitting. With $K_3[Fe(CN)_6]$, however which lacks one electron for

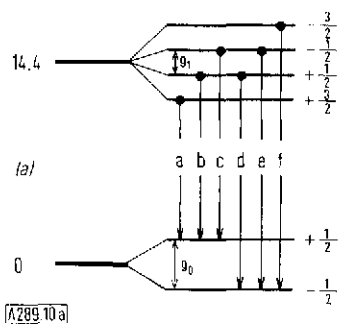
completing the remaining 3d-orbitals, splitting occurs, which, like that of the iron(II) ion (there is an electron deficiency in place of one electron outside the completed shell), is strongly influenced by temperature. For nitrosylprussiate, on the other hand, the marked splitting observed is practically independent of temperature, as is to be expected from a complex ion with completed shells, in view of the symmetrical arrangement in question.

e) Magnetic Splitting

In the magnetic field produced by the crystal field and the electron shell around the nucleus, the excited state of ^{57}Fe is split up into four energy levels, the ground state into two levels (Fig. 10). The six possible transitions between the levels of the excited and ground states, arising from consideration of the selection rule

$$\Delta m = 1, 0, \text{ or } -1$$

result in six resonance lines in the spectrum (Fig. 10b). The splitting of the ground state of ^{57}Fe amounts to $g_0 = 3.96$ mm/sec.



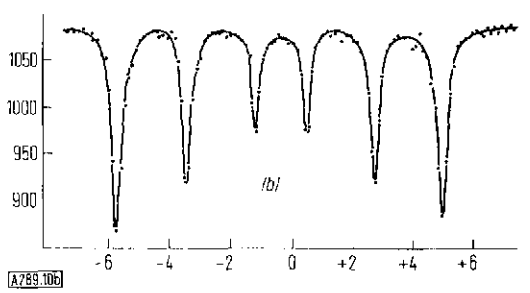


Fig. 10. (a) Energy-level diagram for magnetic splitting of the ground state and the first excited state of ^{57}Fe in metallic iron.
(b) Mössbauer spectrum of metallic iron.
Ordinate: transmission [arbitrary units]
Abscissa: velocity of the source relative to the absorber [mm/sec]

f) Examples of Applications

α) *Prussian Blue*

The structure and color of Prussian Blue have been subjects of speculative discussion for many years. "Insoluble Prussian Blue" is formed on treating a solution of potassium ferrocyanide, $K_4[Fe(CN)_6]$, with an excess of a solution of Fe^{3+} ions. It has the overall composition $Fe_4[Fe(CN)_6]_3$. Examination of the compound with the aid of the Mössbauer effect showed that, contrary to earlier assumptions, definite levels of oxidation, *viz.* the oxidation levels +2 and +3, can be ascribed to the iron atoms. The deep color of Prussian Blue cannot therefore be attributed to oscillating valencies or to resonance of the type

$$Fe^{II}(CN)_6Fe^{III} \leftrightarrow Fe^{III}(CN)_6Fe^{II}.$$

Recently, *Robin* [18] reached the same conclusion as a result of investigation of absorption spectra of "soluble Prussian Blue". Figure 11a shows the Mössbauer spectrum of "insoluble Prussian Blue". It is produced by superimposing the dashed curves. Curve 1 is characteristic for $[Fe(CN)_6]^{4-}$, while the spectrum composed of curves 2 and 3 corresponds to quadrupole splitting with

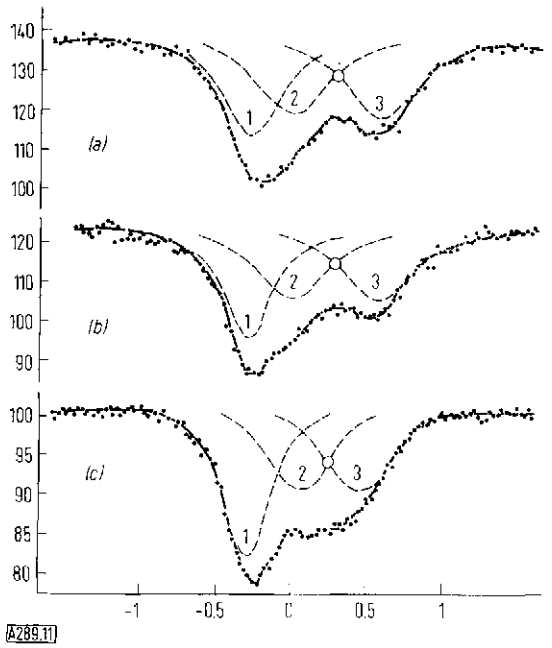


Fig. 11. Mössbauer spectra of (a) insoluble Prussian Blue, (b) Turnbull's Blue, (c) soluble Prussian Blue at −130 °C.
Ordinates: transmission [arbitrary units]
Abscissa: velocity of the source relative to the absorber [mm/sec]

the isomeric shift characteristic for Fe^{3+} ions. The ratio of the areas below the curves 1 and (2+3) is 3:4 within the limits of accuracy [*] and corresponds to the numerical ratio of the iron atoms with the oxidation levels +2 and +3.

"Turnbull's Blue" gives the spectrum shown in Figure 11b. This compound is formed by mixing a solution of potassium ferrocyanide with an excess of a solution of Fe^{2+}. It can be assumed from the similarity of its spectrum with that of "insoluble Prussian Blue" that, on mixing the solutions, the reaction

$$Fe^{2+} + [Fe^{III}(CN)_6]^{3-} \rightarrow Fe^{3+} + [Fe^{II}(CN)_6]^{4-}$$

occurs. This is also to be expected from the redox potentials of the ions.

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[18] *M.B. Robin*, Inorg. Chem. *1*, 337 (1962).

[*] The method used by the authors for resolving the spectrum into individual lines permits accurate determination of energies, but yields the intensities with an accuracy of only 30%. The ratio of the intensities of the lines 1:(2+3) in Figure 11a does not correspond accurately to the postulated ratio 3:4. However, the mean intensity ratio of the lines obtained from numerous spectra of Prussian Blue amounted to 0.72 and therefore approximated very closely to the theoretical value of 0.75.

On mixing solutions of either $K_4[Fe(CN)_6]$ and Fe^{3+} salts or of $K_3[Fe(CN)_6]$ and Fe^{2+} ions in a molar ratio of 1:1, "soluble Prussian Blue" of composition $KFe[Fe(CN)_6]$ is obtained in colloidal form. The Mössbauer spectrum of "soluble Prussian Blue" is shown in Figure 11c. Curve 1 corresponds to the ferrocyanide ions that are also present in this compound, and the doublet (curves 2 and 3) to the Fe^{3+} ions. The areas under the curves 1 and (2+3) are in a ratio of 1:1, corresponding to the ratio of Fe^{II} and Fe^{III} in the compound. This is therefore potassium iron(III) ferrocyanide.

On the basis of the structure proposed by *Keggin* [19] for "soluble Prussian Blue" (Fig. 12), it can be concluded from the results of our investigations that, if any bonds at all are formed between the nitrogen and iron, they can only be very weak and iron of oxidation number +3 is present largely in the ionized form. An X-ray analysis of "soluble Prussian Blue" would be of interest. Magnetic susceptibility determinations, too, tally with our data. "Soluble Prussian Blue" has a magnetic moment of 5.72 Bohr magnetons per $KFe[Fe(CN)_6]$ molecule. This moment corresponds to five unpaired electrons per formula unit, as is to be expected in the presence of a free Fe^{3+} ion.

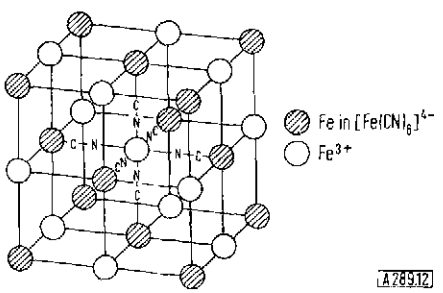


Fig. 12. Structure of "soluble Prussian Blue". The potassium ions are arranged tetrahedrally around the central iron ion.

It is noteworthy in this connection that copper(II) and silver ferrocyanide also show unresolved resonance lines with an isomeric shift almost identical with that found for $K_4[Fe(CN)_6]$ or with the line arising from $[Fe(CN)_6]^{4-}$ in $Fe_4[Fe(CN)_6]_3$. Copper(II) and silver ferricyanides both show quadrupole resolutions in the Mössbauer spectrum, that vary considerably with temperature, as is typical for $[Fe(CN)_6]^{3-}$.

β) *Prussiates*

Prussiates are compounds in which one cyano group of the ferrocyanide ion has been replaced by a different ligand, *e.g.* by NO^+ in sodium nitrosylprussiate, $Na_2[Fe^{II}(CN)_5NO]$, or by NH_3 in sodium aminoprussiate, $Na_3[Fe(CN)_5NH_3]$. The Mössbauer spectrum of the former compound consists of a doublet, the components of which show wide splitting (ε = 1.723 mm/sec at room temperature). Its quadrupole splitting proved to be virtually independent of temperature. Similar quadrupole splittings of varying magnitude are encountered with other prussiates. The isomeric shifts of the prussiates fall within the range typical for complex compounds. Their magnitude is characteristic for the nature of the bond between the ligand and the central iron atom.

[19] *O. F. Keggin* and *F. D. Miles*, Nature (London) *137*, 577 (1936).

As described in the preceding section, $[Fe(CN)_6]^{4-}$ shows only one single resonance line. On account of its octahedral symmetry, the electric field gradient and therefore the quadrupole splitting equal zero. The charge distribution is non-spherical for the prussiates, however, *i.e.* a finite field gradient is to be expected. This can have a positive or negative sign, according to the nature of the bond to the ligand that has replaced a CN-group.

In ferrocyanide, $[Fe(CN)_6]^{4-}$, the cyano groups are attached to the central iron atom by σ-bonds. In addition, each bond has a partial π-bond character which inhibits the high negative charge on the iron ("back-donation"). These bonds are illustrated in Figure 13.

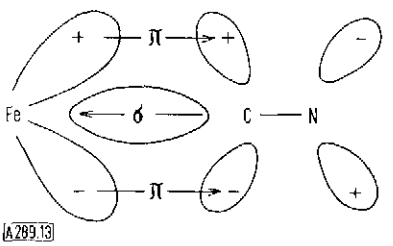


Fig. 13. Diagrammatic representation of the bond between an iron ion and a ligand with a π-orbital.

They hold in principle for all stable complexes. Charge is removed from the central atom by the π-bond, the system then conforming to Pauling's electroneutrality principle, according to which the charge on the central atom should never exceed +1 or −1. As a result of this type of bond, which recurs in all highly stable complexes, the isomeric shifts in Mössbauer spectra fall within a limited range around the position to be expected for Fe^0.

If a cyanide group in $[Fe(CN)_6]^{4-}$ is replaced by another ligand in which the π-bond character is stronger, *e.g.* NO^-, then the electron density of the 3d-orbital, from which the electrons used for the π-bond originate, is reduced. Accordingly, the lines of the nitrosylprussiate ion are shifted into negative δ-values, relative to that of the ferrocyanide ion. If a cyano group is replaced by the ligand NH_3 or NO_2^-, which cannot form π-bonds, the reverse effect occurs. A shift toward higher δ-values, relative to $[Fe(CN)_6]^{4-}$, is observed. A weak π-bond is to be expected in the sulfite complex, $[Fe(CN)_5SO_3]^{5-}$, as only the more diffuse d-orbitals of sulfur are now available for π-bonding. The isomeric shifts of the prussiates accordingly occur with decreasing strength of the π-bonding of the non-cyano ligand

$$NO^+ \gg CN^- > SO_3^{2-} > NO_2^- \approx NH_3$$

at increasingly positive values of δ. Nitrito- and ammino-prussiates have the same isomeric shift.

The σ-donor effect of the ligand has not been taken into consideration in these explanations. This seems permissible, as a small change in the σ-donor effect has only a minor influence on the total s-electron density, especially as this concerns a hybrid in which s-electrons play a subordinate part. The fact that the shifts for the prussiates depend on the nature of

bonds to the ligands shows that the three π-bonds present in octahedral complexes are not distributed over the remaining five cyano groups, if the sixth group is unable to enter into a π-bond, but that the proportion of π-bond character is then reduced.

Formation of a stronger π-bond with the sixth ligand, compared to CN^-, results in a positive field gradient, a weaker π-bond in a negative one. According to what has been explained above, a positive field gradient is to be expected from the compounds tested only with nitrosyl prussiate, $[Fe(CN)_5NO]^{2-}$, and a negative field gradient in all other cases.

γ) *Iron Carbonyls*

There are three known iron carbonyls, *viz.* iron pentacarbonyl, $Fe(CO)_5$, di-iron enneacarbonyl, $Fe_2(CO)_9$, and tri-iron dodecacarbonyl, $Fe_3(CO)_{12}$. The structures of the first two compounds [20, 21] are reproduced in Fig. 14. In iron pentacarbonyl, the five CO groups are

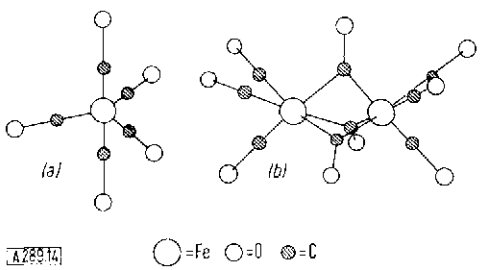


Fig. 14. Structure of (a) iron pentacarbonyl and (b) di-iron enneacarbonyl.

arranged at the corners of a trigonal bipyramid. The σ-bond system arises via $d_{z^2}sp^3$-hybridization, while the eight electrons in the d_{xy}-, d_{xz}-, d_{yz}-, and $d_{x^2y^2}$-orbitals are used for forming π-bonds from the iron to the CO ligands. In a way similar to that described in the preceding section, the π-bonds circumvent a high negative charge on the central iron atom.

The trigonal bipyramidal arrangement of the ligands results in a finite electric field gradient around the central iron atom, which is reflected in splitting of the resonance line of the iron. The Mössbauer spectrum of $Fe(CO)_5$ (Fig. 15a) consists of two lines, the distance between them corresponding to a quadrupole splitting of 2.53 mm/sec at −133 °C. The isomeric shift is −0.47 ± 0.08 mm/sec at −133 °C. It is noteworthy in this spectrum that the left-hand component of the doublet is smaller than the right-hand one. By rotating the test substance, *Kalvius* et al. showed that this arises from preferential orientation of the molecular field relative to the direction of radiation and were able to conclude that both the field gradient and quadrupole moment have positive values. Preferential orientation of this kind occurs easily on solidification of $Fe(CO)_5$ (m.p. −21 °C). Variations in the freezing procedure result in variations

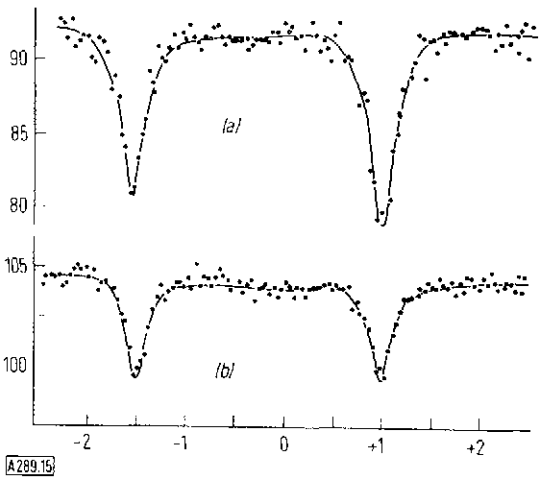


Fig. 15. Mössbauer spectrum of $Fe(CO)_5$ (a) in the solid state and (b) in a frozen solution.
Ordinate: transmission [arbitrary units]
Abscissa: velocity of the source relative to the absorber [mm/sec]

in the relative intensities of the pair of lines. On the other hand, when using solidified solutions of $Fe(CO)_5$ in tetrachloroethane, the authors obtained a pair of lines with equal intensities (Fig. 15b). It is reasonable to suppose that a homogeneous phase is also present in solution.

Two important applications arise from the fact that the Mössbauer effect can also be measured in solidified solutions: 1. It is possible to examine molecules or ions independently of the influences of a crystal lattice. 2. It is also possible to examine substances that cannot be isolated in solid form or are only stable in solution.

In di-iron enneacarbonyl, $Fe_2(CO)_9$, each iron atom is surrounded approximately octahedrally by carbonyl groups; it may therefore be supposed that the σ-bond system is formed by $d^2_{e_g}sp^3$-hybridization. Each iron atom accepts two electrons from the corresponding terminal carbonyl groups and one from each of the bridging CO groups, so that each iron atom has 17 outer electrons, including its own eight outer electrons, available. Since the compound is diamagnetic, the two "lone" electrons have to couple their spins somehow. The relatively short iron-iron distance observed on examination of the crystal led to the assumption that a covalent iron-iron bond was present. The result of the authors' investigation gives preference, however, to a suggestion by *Orgel* [22], according to which even a weak coupling of the unpaired spin, as might be effected, for example, through the carbonyl bridges, would suffice to explain the diamagnetism of $Fe_2(CO)_9$. The Mössbauer spectrum of di-iron enneacarbonyl is shown in Fig. 16. It shows a slight quadrupole splitting, as would be expected in view of the symmetrical surrounding of the iron atoms. The components of the doublet are of unequal size and have an intensity ratio yielding a positive sign for the field gradient (see below).

The structure of tri-iron dodecacarbonyl, $Fe_3(CO)_{12}$, is still unexplained. While *Mill* [23] believes on the basis

[20] *R. V. G. Ewens* and *M. Lister*, Trans. Faraday Soc. *35*, 681 (1939).

[21] *H. M. Powell* and *R. V. G. Ewens*, J. chem. Soc. (London) *1939*, 286.

[22] *L. E. Orgel:* An Introduction to Transition-Metal-Chemistry: Ligand-Field Theory. Methuen, London 1960.

[23] *D. S. Mills*, Chem. and Ind. *1957*, 73.

of his infrared spectroscopical investigation that, of the repeatedly discussed tentative structures *(1)* and *(2)*, he can exclude the latter, *Dahl* and *Rundle* [24] consider

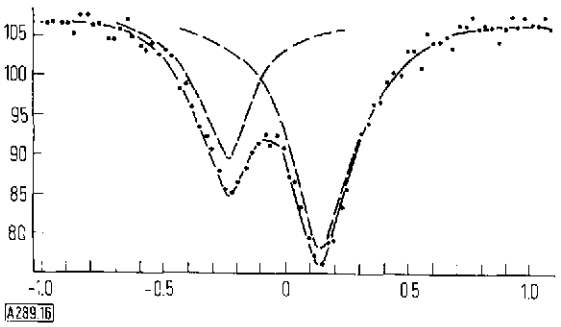
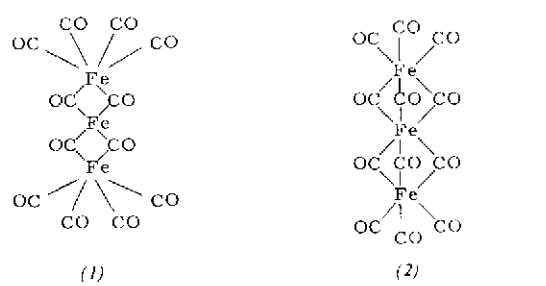


Fig. 16. Mössbauer spectrum of $Fe_2(CO)_9$.
Ordinate: transmission [arbitrary units]
Abscissa: velocity of the source relative to the absorber [mm/sec]

that the view of many authors, according to which the three iron atoms are arranged in linear fashion, is incorrect. They propose a structure in which the iron atoms are situated at the corners of a triangle.



(1) *(2)*

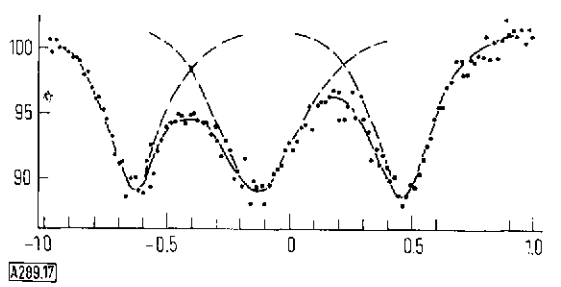


Fig. 17. Mössbauer spectrum of $Fe_3(CO)_{12}$.
Ordinate: transmission [arbitrary units]
Abscissa: velocity of the source relative to the absorber [mm/sec]

The Mössbauer spectrum of this compound is shown in Figure 17. It consists of three lines, the two outer ones corresponding. The quadrupole splitting computed from their distance apart amounts to 1.09 mm/sec. The middle line is somewhat wider than the two outer lines; this may be attributed to a slight partial quadrupole splitting. This spectrum can only be interpreted on the basis of a structural model in which the iron atoms are arranged in a linear fashion and the two outer iron atoms are equivalent to each other. Only structural formula *(1)* can be readily reconciled with the results of our investigations and with the diamagnetism of the compound. The outer iron atoms are arranged octahedrally in this structure, while the central iron atom makes use of a tetrahedral d^3s-hybrid for its bonding. Accordingly, a positive field gradient and consequent splitting of the resonance line are to be expected for the two outer iron atoms, at which four terminal CO groups are situated opposite two bridging CO groups, while the iron atom at the centre of the tetrahedron should yield a single resonance line. The slight broadening of the middle line in the spectrum of tri-iron dodecacarbonyl can be easily understood as a result of a slight distortion of the tetrahedral bonds.

In the hypothetical structural formula *(2)*, all three iron atoms would use d^2sp^3-hybrids for the formation of their bonds, so that the t_{2g}-orbitals of each iron atom would be occupied by only four electrons. This somewhat uneven disturbance of the octahedral symmetry at the inner iron atom and the outer ones would lead to a different splitting of the 3d-electronic terms; this would explain the occurrence of a quadrupole splitting that varies markedly with temperature (as actually observed) for the outer iron atoms, and of a very small one for the inner iron atom. This electronic configuration, however, does not give any explanation for the diamagnetism of the compound.

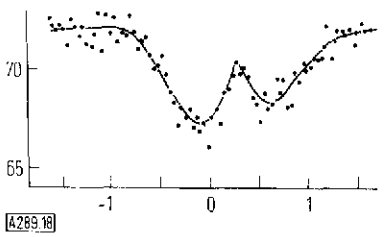


Fig. 18. Mössbauer spectrum of $Fe(CO)_4I_2$.
Ordinate: transmission [arbitrary units]
Abscissa: velocity of the source relative to the absorber [mm/sec]

Figure 18 shows the Mössbauer spectrum of $Fe(CO)_4I_2$. In this case, in contrast to the spectrum of $Fe(CO)_5$, the left-hand line is larger than the right-hand one. This phenomenon again arises from the fact that the crystals are preferentially orientated, a phenomenon that can also arise in crystal powders and is known from X-ray investigations. If the spectrum line corresponding to the state with $m = \pm 3/2$ occurs at higher velocities than the one corresponding to the state with $m = +1/2$, the field gradient is positive, and negative in the reverse case; cf. [9, 10].

δ) *Potassium Ferrate(VI), Potassium Ferrate(III), and Potassium Dithioferrate(III)*

The Mössbauer spectrum of potassium ferrate(VI), K_2FeO_4, shows an unsplit resonance line, shifted far to the left, with a δ-value of about −1.20 mm/sec at −120 °C. Because of the tetrahedral symmetry of the complex ion $[FeO_4]^{2-}$, no quadrupole splitting occurs. It can be seen from the position of the absorption line and from the absence of splitting, which of the two possible bond hybrids, orientated towards the corners of a tetrahedron, are being used for the π-bond system. For an sp^3-hybrid, a δ-value considerably lower than the one observed would be expected according to the calculations of *Watson* [25]. The 3d-orbitals of iron

[24] *L. F. Dahl* and *R. E. Rundle*, J. chem. Physics *26*, 1751 (1957); see also *ibid. 27*, 323 (1957).

[25] *R. E. Watson* and *A. J. Freeman*, Physic. Rev. *123*, 2027 (1961).

would then be occupied by only two electrons so that the screening effect on the s-electron density would be negligible. *Wertheim* and *Herber* reached the same conclusion. Moreover, splitting varying with temperature should be observed in the presence of sp^3-hybrids.

In potassium ferrate(III), each iron atom is surrounded tetrahedrally by four oxygen atoms. The tetrahedra are joined together along the edges. The δ-value of potassium ferrate(III) is only about 0.2 mm/sec less than $\delta_{Fe^{3+}}$, *i.e.* the s-electron density in ferrate(III) is not much higher than that in the Fe^{3+} ion. In any case, the slight shift is caused by the contribution made by the sp^3-hybrid towards the s-electron density, as the bonds between the oxygen and the iron are pure σ-bonds. The fact that the contribution of the sp^3-hybrid is as small as it is must probably be due to the fact that a hybridized 4s-electron increases the s-electron density to a less extent than a normal 4s-electron and that the bonds have become strongly heteropolar.

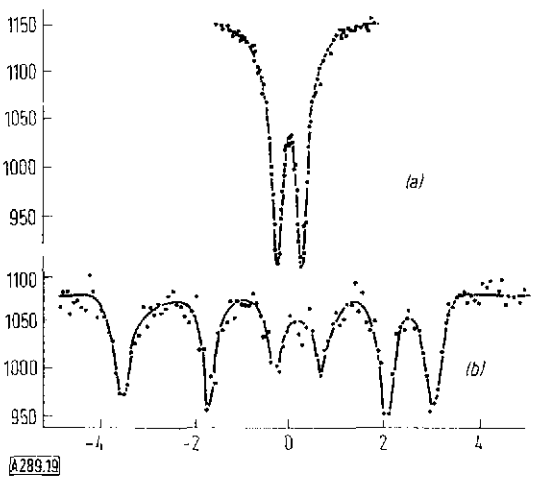


Fig. 19. Mössbauer spectrum of $KFeS_2$ (a) at 25 °C and (b) at −145 °C.
Ordinate: transmission [arbitrary units]
Abscissa: velocity of the radiation source relative to the absorber [mm/sec]

The Mössbauer spectrum of potassium dithioferrate(III) at 25 °C and −145 °C is shown in Fig. 19. Only quadrupole splitting occurs at room temperature. The fact that, apart from magnetic dissociation, quadrupole interaction also exists even at low temperatures, is seen from the unequal shifts of the outer pairs of lines, which should be equal in length for purely magnetic splitting. Figure 20a illustrates the splitting of the 14.4 keV level of the ^{57}Fe nucleus diagrammatically. As a result of quadrupole interaction, the levels with $m = \pm 1/2$ are raised by $\varepsilon/2$, to a first approximation, and those with $m = \pm 3/2$ lowered by $\varepsilon/2$. Magnetic splitting of the level yields six lines, which, in the case of simultaneous quadrupole interaction, lead qualitatively to the theoretical spectrum represented in Figure 20b.

The splitting g_0 of the ground state follows directly from the spectrum as the distance between lines 4 and 2 or 5 and 3. The shift can be determined by working out the arithmetic mean of the positions of lines 1, 2, 5, and 6 or of 1, 3, 4, and 6 and determining the distance from this mean to the position of velocity = 0. From the splitting of the ground state of ^{57}Fe in $KFeS_2$ follows the

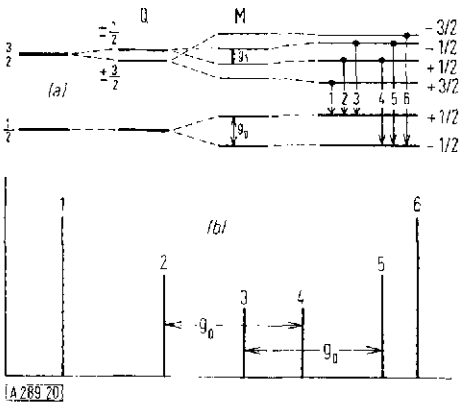


Fig. 20. (a) Energy-level diagram for superimposing quadrupole splitting (Q) and magnetic splitting (M).
(b) corresponding spectrum to a first approximation.
Ordinate: relative intensity
Abscissa: energy.

magnetic field around the nucleus, via the known splitting of the ground state in metallic iron and its known internal magnetic field.

ε) *Other Compounds*

α-Dipyridyl reacts readily with ferrous chloride to form the complex $Fe(dipyr)_3Cl_2$. Its bonding arrangement resembles that of ferrocyanide. The σ-bond system is a d^2sp^3-hybrid. Back-donation of charge from the iron atom to the ligands is rendered possible by delocalized π-orbitals. The Mössbauer spectrum of the compound indicates slight quadrupole splitting which is virtually independent of temperature and in which the octahedral symmetry, which is somewhat disturbed by the bifunctional ligands, becomes apparent.

Quadrupole splitting that is also largely independent of temperature is found in the spectra of pyrite and marcasite, the bisulfides of iron, FeS_2. The shifts of the two compounds show that iron is not present at the oxidation level +4, but at +2, as is also implied from magnetic determinations by *Klemm*. Besides, the shift falls within the range typical for complex compounds. In these two compounds, too, iron uses largely a d^2sp^3-hybrid for the formation of its bonds. The bonds have markedly covalent character. Pyrite has a sodium chloride type lattice in which the chloride ions have been replaced by the centre of gravity of a dumbbell formed by two sulfur atoms (S–S distance = 2.14 Å). The slight deviation from octahedral symmetry around the iron atoms causes the slight quadrupole splitting mentioned above.

The authors wish to thank Prof. Dr. M. Becke-Goehring and Prof. Dr. O. Haxel for their interest in these investigations.

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Mass Transport in Metallic Solids [*]

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Mass transport in a metallic solid requires that the lattice units exchange places. This is made possible by lattice defects. Also, a circular interchange has to be discussed. Driving forces cause the superposition of directional motion over the random motion of site exchange: When a chemical potential gradient exists, isothermal diffusion occurs; with an electrical potential gradient, electrolytic transport takes place; and with a temperature gradient, the effect is thermal diffusion. Both concentrational changes and dimensional changes may accompany these processes. From observation of these phenomena, the mechanism by which lattice particles change places can be deduced. In addition, it is possible to calculate characteristic data, such as migration energy, imaginary charge, and heat of transportation.

Site Exchange Mechanisms

As a rule, metals and alloys crystallize in highly symmetrical structures, in which face-centered cubic, body-centered cubic, and hexagonal close-packed lattices predominate. Macrocrystals consist of arrays of mutually disorientated regions, the so-called grains, with sizes and forms that depend strongly on the history of the material. The grains in themselves are crystallographically uniform, but by no means free of defects. Atomic-scale point defects are most important for mass transport processes. A vacancy is an unoccupied lattice

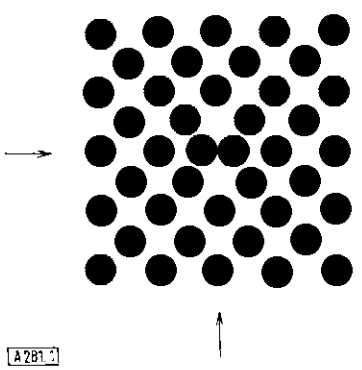

Fig. 1. Interstitial atom in a cube face of a face-centered cubic lattice; dumbbell arrangement.

(The lattice distortion around the dumbbell is quite difficult to represent in the model. It is actually considerably greater than it appears here. In the transport process, one of the dumbbell atoms changes places with a neighboring atom so that the dumbbell arrangement is passed on.)

point, whereas an interstitial atom occupies a position between the lattice sites (Fig. 1). Linear lattice defects like screw and edge dislocations are also of interest (Fig. 2). These often exhibit jogs (Fig. 3), which can move from one lattice point to another (climb of the dislocation). Depending on the direction of the climb, vacancies are either filled up or are newly formed. Furthermore, vacancies can also be filled or created at the grain boundaries or at the outer surfaces. This

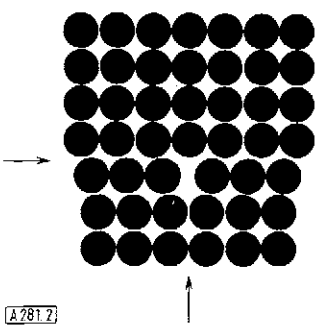

Fig. 2. Edge dislocation.

mechanism does not take place within the domain of a defect-free lattice. The number of dislocations and interstitial atoms in a metal is a function of the previous

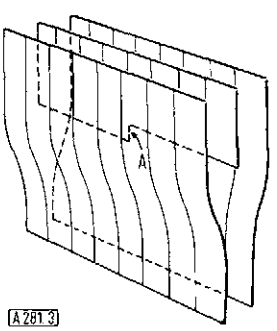

Fig. 3. Jog (A) in an edge dislocation. From [1]. The distribution of the atoms in the front is shown in Fig. 2

treatment of the material. The vacancies are in thermal equilibrium with the lattice. The following equation gives their number $N_{\square}$ [1]:

$$N_{\square} = N \cdot \exp(S^{f}_{\square}/R) \cdot \exp(-H^{f}_{\square}/RT) \qquad (a)$$

where N = total number of atoms, $H^{f}_{\square}$ = enthalpy of vacancy formation, and $S^{f}_{\square}$ = entropy of vacancy formation.

[*] Reported in part at a meeting of the Gesellschaft Deutscher Naturforscher und Ärzte and of the Gesellschaft Deutscher Chemiker in Munich on September 12th, 1962.

The equilibrium is dynamic; *i.e.*, vacancies are continually being filled up and new ones created. Their average lifetime is a function of temperature as well as of the number of vacancy sources and sinks. Tables 3 and 4 give typical values for $H^f_{\square}$.

Maxwellian statistics apply to the distribution of energies in a metal crystal. In general, the number of atoms (N_E) with energy greater than E (in eV) is given by

$$N_E = N \cdot \exp(-E/kT) \qquad (b)$$

where N = total number of atoms and k = Boltzmann's constant

The elementary process of transport of matter is the interchange of lattice units. This can be accomplished by the following mechanisms:

a) *Direct Interchange*: Two lattice atoms exchange their sites directly (Fig. 4). This process requires a very substantial lattice distortion and an unusually large

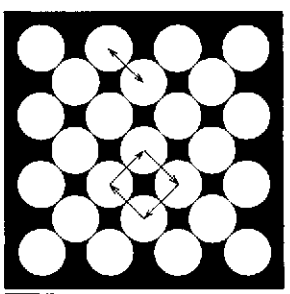

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Fig. 4. Cube face of a face-centered cubic lattice. Indication of a direct interchange and a cyclic interchange.

activation energy. In practice, such a magnitude of activation energy cannot be induced in a solid by thermal means alone [2].

b) *Cyclic Interchange (Ring of Four)*: Here, not two, but four lattice atoms exchange sites simultaneously (Fig. 4). The lattice deformation required for this process is significantly smaller, and the activation energy is therefore lower. For body-centered cubic metals this mechanism, as well as the vacancy mechanism discussed below, are possible [3]. So far, cyclic interchange has never been demonstrated with certainty in any case. Perhaps it occurs in α-iron.

c) *Mass Transport via Interstitial Atoms*: The atoms can migrate from one interstitial site to another (interstitial mechanism), or interstitial atoms and lattice atoms can exchange places (interstitialcy mechanism). The first case occurs chiefly with occluded foreign atoms such as carbon in iron. In close-packed metals, the interstitialcy mechanism demands large lattice distortion and, therefore, high energy. For this reason, there are no interstitial atoms at thermal equilibrium; they have to be produced, *e.g.*, by irradiation. Thus, processes involving interstitial atoms can occur only at non-equilibrium. The interstitial atoms return to lattice sites during the transport process. In general, the migration energy is lower than that required for the migration of vacancies [1].

d) *Mass Transport via Vacancies (Vacancy Mechanism)*: Here, interchange between vacancies and lattice atoms takes place. The only activation energy needed is the energy required for the removal of the atoms from the lattice, provided the sites are exchanged in certain preferred directions, *e.g.*, along the face or body diagonal in the case of face-centered cubic lattices. There are twelve equivalent directions in which site exchanges may occur. At temperatures at which sufficient vacancies exist at equilibrium, this is the preferred site exchange mechanism [2].

In a metal crystal at a sufficiently high temperature, these site exchange processes proceed in completely statistical fashion, *i.e.* in no specific direction. Therefore, mass transport occurs only on the atomic and not on the macroscopic scale. The atoms move around completely at random, similar to Brownian motion in a gas. A drift motion is superimposed upon the random motion only when a driving force is applied.

The Driving Force

A driving force always arises from the tendency of the system to attain a state of lowest possible free energy. Essentially, three cases can be distinguished:

a) *The Force Is of a Chemical Nature (Isothermal Diffusion)*

In an isothermal binary system with a unidirectional gradient of chemical potential μ_i

$$\mu_i = \mu_0 + RT \ln a_i \qquad (c)$$

(a_i = thermodynamic activity and μ_0 = basic potential, independent of concentration)

the rate of drift w_i will be

$$w_i = \mathfrak{B}_i \cdot \frac{1}{N_L} \cdot \frac{d\mu_i}{dx} \qquad (d)$$

($\mathfrak{B}_i$ = mobility of the transported lattice particles in cm/dyne/sec x = position coordinate).

By substitution of (c) into (d) and multiplication one obtains

$$w_i = -\mathfrak{B}_i \cdot k \cdot T \cdot \frac{d\ln N_i}{dx} \cdot \frac{\partial \ln a_i}{\partial \ln N_i} \text{ [cm/sec]} \qquad (e)$$

(N_i = mole fraction of component i in the alloy) [4].

b) *The Driving Force Is Electric in Nature (Electrolytic Transport)*

In metallic solids, all lattice particles are electrically charged, since they have given up electrons to the electron gas. An electric field acts on the lattice particles with a force $z \cdot \zeta \cdot e$, where z is the number of electrons

[1] Review, for example, *H. G. van Bueren:* Imperfections in Crystals. North Holland Publishing Comp., Amsterdam 1960; *A. Seeger:* Handbuch der Physik. Springer, Heidelberg 1955, Vol. VII, 1, p. 390 et seq.

[2] *H. B. Huntington* and *F. Seitz*, Physic. Rev. *61*, 315 (1942); *76*, 1728 (1949).

[3] *C. Zener*, Acta crystallogr. *3*, 346 (1950).

[4] Review, for example, *A. D. LeClaire*, Progr. Metal Physics *1*, 336 (1949); *4*, 265 (1953).

yielded per atom, e is the elementary charge, and ζ is the field strength. The factor ζ is a constant < 1 which reflects the shielding of the charge on the atomic residue by the electron gas. Moreover, all the dislocated lattice particles (which actually control the mass transport process) interact with the conduction electrons, so that they are under the influence of an additional force $Z \cdot e \cdot \mathfrak{E}$. The factor Z represents an imaginary charge, which is related to the specific resistance of the transported defect. It is negative in electron-conducting metals and positive in defect-conducting metals. Thus, there results for the migration rate

$$w_i = \mathfrak{B}_i \cdot e \cdot \mathfrak{E} (\zeta z_i + Z_i) \text{ [cm/sec]}. \quad (f)$$

The direction of migration is determined by the sign of $(z_i \cdot \zeta + Z_i)$. As a rule, for pure metals, metallic solid solutions, and the mainly metallic group of Hume-Rothery phases, Z_i is greater than the quantity $z_i \cdot \zeta$ and is therefore direction-determining. A negative sign signifies migration to the anode, a positive sign migration to the cathode [5, 6]. However, not all of the experimental results can be explained unequivocally.

c) *The Force Is Thermal in Nature (Thermal Diffusion)* [7]

In this case, the magnitude of the rate of migration is given by

$$w_i = \mathfrak{B}_i \cdot \frac{Q_i^*}{T} \cdot \frac{dT}{dx} \text{ [cm/sec]} \quad (g)$$

where Q_i^* – heat of transport, *i.e.*, the quantity of heat transported by the migrating lattice particles. A positive heat of transport indicates that the lattice particles move in the direction of the temperature gradient, while a negative heat of transport indicates countermotion. From kinetic considerations, the heat of transport can be associated with the migration energy of the mobile lattice particles. When the defects are in thermal equilibrium

$$Q_i^* = E^f - \beta \cdot E^m + T \cdot \Delta S_i^* \quad (h)$$

where ΔS_i^* is the partial entropy excess for the component i (difference between the actual and ideal mixing entropies), E^f and E^m are the energies of formation and of migration of the lattice defects effecting the transport, and β is a constant which, according to our present knowledge, is approximately +1 for transport *via* vacancies, and remarkably smaller or even negative for transport *via* occluded foreign atoms, *e.g.*, C in Fe. As far as the formation and migration energies are concerned, it is not yet absolutely clear whether they are free energies or total energies, as generally the agreement between theory and experiment is still by no means satisfactory. The paucity of reliable experimental investigations does not allow a positive statement.

All three cases treated above are limiting cases, between which any number of transitions are possible.

[5] Reviews, for example, *Th. Heumann:* Paper 2C in: The Physical Chemistry of Metallic Solutions and Intermetallic Compounds. Symposium NPL No. 9, Her Majesty's Stationery Office, London 1959; *H. Wever:* Habilitation thesis, Technische Universität Berlin, 1958.

[6] *H. B. Huntington* and *A. R. Grone*, Physics Chem. Solids *20*, 76 (1961).

[7] *H. Wever*, Z. Naturforsch., in the press.

A pure metal is a homogeneous material, and therefore no concentration or activity gradients can arise within it. This can only be achieved, if at all, by inclusion of a radioactive isotope. Strictly speaking, however, this then constitutes a two-component system comprising an active and an inactive metal. This case will be considered below.

On the other hand, electrical and thermal forces can occur in pure metals. If a cylindrical metal sample is placed in an axial temperature gradient or in an electric field, a unidirectional driving force acts on the mobile lattice particles. As a result, when any direct or cyclic interchange of the lattice particles occurs, each site exchange in one direction is followed by another in the opposite direction. Hence, this mechanism does not permit unidirectional transport of matter. Although a transport force is certainly present, it is completely ineffectual. Unidirectional transport of matter is thus conceivable only by site exchange *via* point defects. In the case of the vacancy mechanism, each site exchange of a lattice atom is accompanied by an oppositely directed vacancy site exchange. Thus, the flow of matter in one direction also creates a flow of vacancies in the reverse direction and results in a deficiency of vacancies at one end of the sample and an excess at the other. The thermal equilibrium of the defects is disturbed. The metal crystal attempts to re-establish the equilibrium; new vacancies are formed by way of a source of vacancies on the one side, and the excess of vacancies is healed out by means of a sink at the other. This formation of new vacancies means, however, that new lattice defect points arise, and conversely, that the filling-in of vacancies results in the disappearance of lattice defect

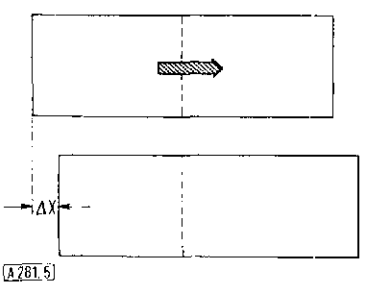

Fig. 5. Mass transport and its effects in a pure metal.
Upper part of figure: Sample before the experiment.
Lower part of figure: Sample after the experiment.
As a result of the mass transport through the plane indicated by the dotted line, its position, relative to the sample ends, changes. For purposes of clarity the magnitude of the effect is greatly exaggerated.

points. Both cause dimensional changes, one in the positive sense and the other in the negative. Thus, one half of the sample becomes shorter (or thinner) and the other half lengthens (or thickens), see Fig. 5. Instead of elimination of the vacancies by a vacancy sink, sometimes agglomerates of vacancies can also be formed, which then grow into macroscopic cavities in the course of time.

The dimensional changes are actually small, but are nevertheless experimentally detectable. At temperatures

100–200 °C below the melting point, linear changes amount to a few thousandths of a millimeter per day. This is related to the limited mobility of atoms in pure metals. The values of $(\zeta \cdot z + Z)$ for electrolytic transport and Q* for thermal diffusion can be determined from measurements of the linear changes. The data available at present are summarized in Tables 1 and 2.

Table 1. Electrolytic transport in metals

Metal	Temperature [°C]	Direction	$z \cdot \zeta + Z$	Ref.
Cu	900	Anode		[8,9]
	>1000	Cathode		[8,9]
Au	850–1000	Anode	2.5–1.5	[6]
Pt	1350–1500	Anode		[10]
	1550–1730	Cathode		[10]
Al		Anode		[11]
Ni	1350	Cathode	ca. 0.15	[14]
γ-Fe	1190–1325	Cathode	60–10	[12]

Table 2. Thermal diffusion in metals

Metal	Direction of mass transport	Q* [eV]	Ref.
Cu	cold	0.16	[13]
Au	warm	0.26	[13]
Pt	cold	0.25	[10]
Ni	warm		[14]
α-Fe	no effect		[15]
Zn	no effect		[16]

The upper part of Fig. 6 shows a sample arranged for the measurement of isothermal diffusion by means of

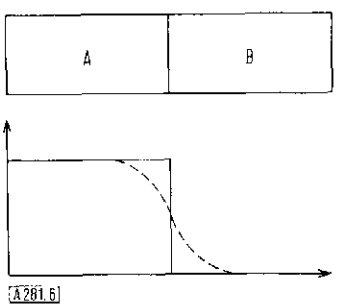

Fig. 6. Isothermal diffusion.
Above: sample before the experiment.
Below: concentration of component A.
before the experiment
– – – after the experiment.
Ordinate: concentration of A.
Abscissa: position coordinate.

radioactive tracers. A is a radioactively doped pure metal, B is the same metal without tracer. The lower part of Figure 6 shows the concentration of the radioactive component before and after the diffusion experiment. The process conforms to Fick's law (i), which gives the flow of component A per second through 1 cm² of interface:

$$I_A = -D^* \cdot \frac{\partial N_A}{\partial x} \quad [cm^3/cm^2/sec] \qquad (i)$$

where D^* is the coefficient of radioactive diffusion, N_A is the local molar fraction of active component, and x is the position coordinate. The diffusion coefficient, which is only a factor of proportionality, may be related to the mobility, introduced in equation (d), by means of the following equation:

$$D^* = k \cdot T \cdot f \cdot \vartheta \quad [cm^2/sec] \qquad (k)$$

where f is a correlation factor [17], which assumes values between 0.1 and 1, depending on the transport mechanism and the lattice structure. Since the concentration gradient flattens out in the course of the experiment, the magnitude of the particle flow also diminishes. The reduction in flow is proportional to the square root of the time ($\sqrt{t}$-law). The diffusion coefficient and the mobility can be determined by various means, for example, from the distribution of active material. This can be described mathematically by a Gaussian error function [18].

The diffusion coefficient depends strongly on the temperature. A simple reflection on the problem will explain the temperature dependency: only those lattice atoms qualify for site exchange which are both adjacent to a vacancy and also have a minimum energy H^m sufficient for separation from their site. The diffusion coefficient will therefore be proportional to the probability of the occurrence of a vacancy next to a lattice atom with an energy that is at least equal to H^m. This probability is given by the product of the number of vacancies and the number of lattice atoms adjacent to them. Thus, D^* is equal to

$$D^* = D_0 \cdot \exp\left(-\frac{H^f_{\square} + H^m}{k \cdot T}\right) \quad [cm^2/sec] \qquad (l)$$

where D_0 = frequency factor. As can be shown by a kinetic derivation, D_0 is related to the lattice constant a, the Debye frequency ν_D, and the activation entropies for the formation ($\Delta S^f_{\square}$) and migration (ΔS^m) of the vacancies [1]. Thus:

$$D_0 = a^2 \cdot \alpha \cdot \nu_D \cdot \exp\left(\frac{\Delta S^f_{\square} + \Delta S^m}{k}\right) \qquad (m)$$

where α is a factor approximately equal to unity for face-centered cubic and body-centered cubic lattices. If it is assumed that the activation entropy originates only from elastic stresses in the vicinity of the detaching atoms, then [19]

$$\frac{\Delta S^f_{\square} + \Delta S^m}{k} = \frac{\lambda \cdot \left(H^f_{\square} + H^m\right)}{T_m} \cdot \frac{d \log \mu_s}{\left(\frac{T}{T_m}\right)} \qquad (n)$$

where λ is an empirical constant (= 0.55 for face-centered cubic metals, = 1 for body-centered cubic

[8] *H. Wever*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *60*, 1170 (1956).

[9] *A. R. Grone*, Physics Chem. Solids *20*, 88 (1961).

[10] *Th. Hehenkamp* and *S. C. Ho*, Bull. Amer. physic. Soc. *4*, 172 (1959).

[11] *H. B. Huntington*, personal communication.

[12] *H. Wever:* Paper 2L in: The Physical Chemistry of Metallic Solutions and Intermetallic Compounds. Symposium NPL No. 9, Her Majesty's Stationery Office, London 1959.

[13] *C. J. Meechan* and *G. W. Lehman*, J. appl. Physics *33*, 634 (1962).

[14] *D. Klemens* and *H. Wever*, unpublished results.

[15] *W. G. Brammer*, Acta metallurg. *8*, 630 (1960).

[16] *P. Shewmon*, J. chem. Physics *29*, 1032 (1958).

[17] See, for example, *C. W. McCombie* and *A. D. Lidiard* Physic. Rev. *101*, 1210 (1956).

[18] *W. Seith* and *Th. Heumann:* Diffusion in Metallen. Springer, Heidelberg 1955.

[19] *C. Wert* and *C. Zener*, Physic. Rev. *76*, 1169 (1949).

Table 3. Diffusion data and energies of formation and migration of vacancies in face-centered cubic metal crystals [20]

Metal	D_0 (found)	D_0 (calc.)	$H^f_{\square}$ (found)	$H^m_{\square}$ (found)	$H^f + H^m$	Q (found)	Ref.
	[cm²/sec]		[eV] ([kcal/mole])				
Cu	0.20	0.24	0.95 (21.9)	1.08 (24.9)	2.03 (46.8)	2.05 (47.1)	[25, 26]
Ag	0.40	0.63	1.01 (23.3)	0.88 (20.3)	1.89 (43.6)	1.93 (44.1)	[26 28]
Au	0.091	0.084	0.98 (22.6)	0.83 (19.1)	1.81 (41.7)	1.81 (41.7)	[26, 29, 30]
γ-Fe	0.18					2.80 (64.5)	[31]
Co	0.83					2.94 (67.7)	[32]
Ni	5.8	9.3				3.02 (69.7)	[33]
Al			0.77 (17.7)	0.65 (15.0)	1.42 (32.7)	1.43 (33.0)	[34–37]
Pt	0.33		1.20 (27.6)	1.48 (34.1)	2.68 (61.7)	2.96 (68.0)	[38, 39]
Pb	0.28	1.1	>0.53 (12.2)			1.03 (24.2)	[34, 40]

metals), μ_s is the shear modulus, and T_m is the melting point. Experimental D_0 values, as well as those calculated from Equations (l) and (m), are summarized in Tables 3 and 4 together with experimental data for Q.

Table 4. Diffusion data and energies of formation and migration of vacancies in body-centered cubic and other metal crystals [20]

Metal	D_0 (found)	D_0 (calc.)	$H^f_{\square}$ (found)	Q (found)	Ref.
	[cm²/sec]		[eV] ([kcal/mole])		
Li	0.39		0.41 (9.45)	0.59 (13.5)	[21, 22]
Na	0.24		0.2 (4.7)	0.46 (10.5)	[23, 24]
K			0.39 (9)		[22]
α-Fe ferrom.	2.0	8.7		2.6 (60.0)	[41]
α-Fe param.	1.9	8.7		2.48 (57.2)	[41]
Cr	0.0001			2.28 (52.7)	[42]
β-Ti				1.75–1.95 (40–45)	[43]
β-Zr	0.00024			1.31 (30.1)	[44]
Nb	12.4			4.6 (105)	[45]
W [a]	0.54			5.3 (120.5)	[46, 47]
γ-U	0.023			1.22 (28.5)	[48]
Mg ∥ [b]	1.0	1.12		1.4 (32.2)	[49]
Mg ⊥ [c]	1.5	0.26		1.41 (32.5)	[49]
Zn ∥	0.13	0.05		0.95 (21.8)	[50]
Zn ⊥	0.58	0.25		1.05 (24.3)	[50]
Cd ∥	0.05	0.003		0.79 (18.2)	[50]
Cd ⊥	0.10	0.13		0.85 (19.7)	[50]
In ∥	2.7			0.81 (18.7)	[51]
In ⊥	3.7			0.81 (18.7)	[51]
Tl ∥	0.40			0.99 (22.9)	[52]
Tl ⊥	0.40			0.98 (22.6)	[52]
α-U	0.002			1.74 (40.0)	[53]
Sn ∥ [d]	8.2			1.11 (24.6)	[54, 55]
Sn ⊥	1.4			1.01 (23.3)	[54]

[a] H^m (found) = 1.7 eV (39.2 kcal/mole).
[b] ∥ = direction of diffusion parallel to the c-axis.
[c] ⊥ = direction of diffusion perpendicular to the c-axis.
[d] $H^f_{\square}$ (found) = 0.51 eV (12.0 kcal/mole); H^m (found) = 0.68 eV (15.9 kcal/mole).

Mass Transport in Mixed Phases

The treatment of mass transport in mixed phases will be limited to the most important practical case of two-component systems. In Figures 6, A and B are now taken to represent two different metals. In many respects the relationships remain similar to those described in the preceding section; however, there are two fundamental differences:

(a) Chemical forces (attracting or repellent forces) are now operative between the two components.

[20] Several values are taken from Table III in *D. Lazarus*, Solid State Physics *10*, 116 (1960).

[21] *A. N. Naumov* and *G. Ya. Ryskin*, Zh. techn. Fiz. *29*, 189 (1959).

[22] *D. K. C. MacDonald:* Reports of the Conference on Defects in Crystalline Solids 1954. Physical Soc., London 1955, p. 383.

[23] *H. H. Nachtrieb, E. Catalano*, and *J. A. Weil*, J. chem. Physics *20*, 1185 (1952).

[24] *F. J. Bradshaw* and *S. Pearson*, Proc. physic. Soc. *69*, 441 (1956).

[25] *A. Kuper, H. Letaw, L. Slifkin, E. Sonder*, and *C. Tomizuka*, Physic. Rev. *96*, 1224 (1954); *98*, 1870 (1955).

[26] *W. Schüle, A. Seeger, F. Ramsteiner, D. Schumacher*, and *K. King*, Z. Naturforsch. *16a*, 323 (1961).

[27] *C. T. Tomizuka* and *E. Sonder*, Physic. Rev. *103*, 1182 (1956).

[28] *S. D. Gertsriken* and *N. N. Novikov*, Fiz. Metallov y Metallovdenye *9*, 224 (1960).

[29] *S. M. Makin, A. H. Rowe*, and *A. D. LeClaire*, Proc. physic. Soc. *70*, 545 (1957).

[30] *J. E. Bauerle* and *J. S. Koehler*, Physic. Rev. Letters *2*, 145 (1959).

[31] *F. S. Buffington, K. Hirano*, and *M. Cohen*, Acta metallurg. *5*, 434 (1961).

[32] *H. W. Mead* and *C. E. Birchenall*, Trans. Amer. Inst. Mining metallurg. Engr. *203*, 994 (1953).

[33] *A. Messner, R. Benson*, and *J. E. Dorn*, Amer. Soc. Metals Preprint (1960).

[34] *R. Feder* and *A. S. Nowick*, Physic. Rev. *109*, 1959 (1958).

[35] *R. O. Simmons* and *R. W. Balluffi*, Physic. Rev. *117*, 52, 62 (1960).

[36] *W. DeSorbo* and *D. Turnbull*, Physic. Rev. *115*, 560 (1959).

[37] *A. S. Nowick*, J. appl. Physics *22*, 1182 (1951).

[38] *G. L. Bacchella, E. Germagnoli*, and *S. Granata*, J. appl. Physics *30*, 748 (1959).

[39] *G. V. Kidson* and *R. Ross:* Radioisotopes in Scientific Research. Pergamon Press, London 1957, Vol. I, p. 185.

[40] *R. E. Hoffman, F. W. Pikus*, and *R. A. Ward*, Trans. Amer. Inst. Mining metallurg. Engr. *206*, 483 (1956).

[41] *F. S. Buffington, K. Hirano*, and *M. Cohen*, Acta metallurg. *5*, 434 (1961).

[42] *H. W. Paxton* and *E. G. Gondolf*, Arch. Eisenhüttenwes. *30*, 55 (1959).

[43] *R. F. Peart* and *D. H. Tomlin*, Acta metallurg. *10*, 123 (1962).

[44] *G. Kidson* and *J. McGurn*, Canad. J. Physics *39*, 1146 (1961).

[45] *R. Resnick* and *L. S. Castleman*, Trans. Met. Soc. Amer. Inst. Mining metallurg. Engr. *218*, 307 (1960).

[46] *W. Danneberg*, Metall *15*, 977 (1961).

[47] *L. A. Neimark* and *R. A. Swalin*, Trans. Met. Soc. Amer. Inst. Mining metallurg. Engr. *218*, 82 (1960).

[48] *S. J. Rothman, L. T. Lloyd*, and *A. I. Harkness*, Trans. Met. Soc. Amer. Inst. Mining metallurg. Engr. *218*, 605 (1960).

[49] *P. G. Shewmon*, Trans. Amer. Inst. Mining metallurg. Engr. *206*, 918 (1956).

[50] *G. A. Shirn, E. S. Wajada*, and *H. B. Huntington*, Acta metallurg. *1*, 513 (1953).

[51] *J. E. Dickey*, Acta metallurg. *7*, 350 (1959).

[52] *G. A. Shirn*, Acta metallurg. *3*, 87 (1955).

[53] *Y. Adda, A. Kiroonenko*, and *Cl. Mairy*, C. R. hebd. Séances Acad. Sci. *253*, 445 (1961).

[54] *J. D. Meakin* and *E. Klokholm*, Trans. Met. Soc. Amer. Inst. Mining metallurg. Engr. *218*, 463 (1960).

(b) The energy required for site exchange between a vacancy and an atom of type A is different from that required for exchange between a vacancy and an atom of type B. That means that each of the two components has a different mobility and, because of equation (i), a different diffusion coefficient.

Consideration of (a) is possible by working from equations (e) and (k) and substituting J_i for $w_i \cdot N_i$. Thus,

$$J_i = -\frac{D_i^*}{f_i} \cdot \frac{dN_i}{dx} \cdot \frac{\partial \ln a_i}{\partial \ln N_i} \quad [\text{cm/sec}]. \qquad (o)$$

Comparison with equation (i) shows that there is no fundamental change, since $\partial \ln a_i / \partial \ln N_i$ only represents a correction factor, which is greater than unity in the case of bonding forces between both components of the alloy, and is less than unity in the case of repelling forces. However, this factor disappears not only for an ideal mixture, but also if Henry's law is satisfied. Besides, the factor is the same for both components of the mixture because of the Duhem-Margules relationship. Moreover, the occurrence of chemical forces stipulates that the diffusion coefficient is dependent on the concentration.

However, the significance of the different mobilities of the two components is much more important. Since $\partial \ln a_1 / \partial \ln N_1 = \partial \ln a_2 / \partial \ln N_2$, the values of the driving force for both components are equal in magnitude, but, because of the different direction of the concentration gradient, they are oppositely directed. Therefore, a different mobility for each component always involves a significantly different flow of matter in both directions (Fig. 7a). For every jump of an atom there is a corresponding migration of a vacancy in the opposite

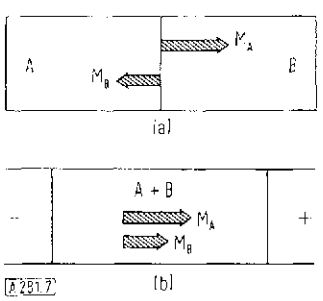

Fig. 7. Flow of matter M_A and M_B (a) for isothermal diffusion of A into B, and (b) for electrolytic transport in an alloy AB.

direction. Thus, the unequal mobility of the two components means that there is also a flow of vacancies (from the right to the left in Fig. 7a) without a driving force acting on the vacancies themselves. The result has already been described for a pure metal. The number of vacancies decreases in one half of the sample and the sample becomes shorter and sometimes thinner. New vacancies are formed in the other half, the sample becoming longer and sometimes thicker (Kirkendall effect) [56]. It can be inferred from Figure 6 that the exchange between A and B atoms occurs at first only in the vicinity of the partition plane and only later does it involve the more remote regions of the sample. The dimensional changes manifest themselves especially in a displacement of the original partition plane relative to

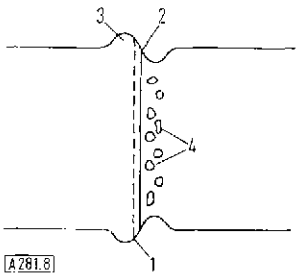

Fig. 8. Schematic representation of the results of the Kirkendall effect during isothermal diffusion.
1. Welding plane before the experiment.
2. Welding plane after the experiment.
3. Swelling.
4. Holes.

the unchanged edge of the sample, as well as in the formation of a swelling on one side and a constriction on the other (Fig. 8). The latter is frequently accompanied by a band of holes. Here the vacancies have accumulated, instead of becoming equally distributed throughout the lattice, so that in the course of time macroscopic, visible holes have been formed [57].

In the case of electrolytic transport, the different mobilities of both components also manifest themselves, but in another way. In Figure 7b, the sample consists of a homogeneous alloy of A and B. Moreover, the temperature of the entire sample is uniform. The driving force can then only be an electric field. As a rule, these forces differ for the two components because $(z_i \cdot \zeta + Z_i)$ is of different magnitude, but they are generally of the same direction in metallic systems. Both components then migrate in one direction, but since their mobilities differ, the fraction of each component in the overall flow of matter is different. The overall flow, which is associated with a corresponding flow of vacancies of equal magnitude but of opposite direction, leads to dimensional changes (by way of the mechanism already described above) which can be much greater than those resulting from isothermal diffusion. Whereas in isothermal diffusion these changes are the result of the difference in two mass flows, in electrolytic diffusion the changes are caused by the sum of two flows. The unequal participation in the overall flow of material results, in addition, in a separation which manifests itself at the ends of the sample [58].

For example, the β-phase (a β-Hume-Rothery phase) in the Cu–Al system shows a mobility several orders of magnitude higher than that of copper. If this phase is subjected to electrolysis between copper electrodes, then practically the case illustrated in Figure 7b is obtained, *i.e.*, matter is transported only within the phase. The phase boundary at the copper or the solid solution being

[55] *W. DeSorbo*, Physics. Chem. Solids *15*, 7 (1960).

[56] *A. D. Smigelskas* and *E. O. Kirkendall*, Trans. Amer. Inst. Mining metallurg. Engr. *171*, 130 (1947).

[57] *Th. Heumann* and *A. Kottmann*, Z. Metallkunde *44*, 139 (1953).

[58] *H. G. Feller*, *H. Wever*, and *Chr. Wilk*, Z. Naturforsch., in the press.

[59] *W. Seith* and *H. Wever*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *57*, 891 (1953).

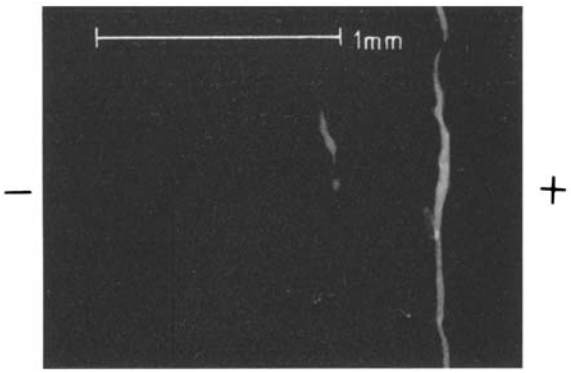

Fig. 9. Dimensional changes induced by electrolytic transport. Carbon-coated sample after flow of 17 faradays at 895 °C. From [59]. Left: β-CuAl. Light stripe: new lattice planes. Right: Cu.

formed from copper and the alloy corresponds to the sample boundary represented in Figure 7b. Figure 9 shows the result of such an electrolytic experiment. Before the experiment, the sample was coated with carbon black. Because of the combined transport of matter towards the anode, new lattice planes arise at the phase/copper boundary. As a result, the carbon layer is rent.

In the case of thermal diffusion, the relationships resemble those for electrolytic transport, but with the additional complication that here both the driving force and the mobility vary along the sample. These relationships are most evident in the case of a symmetrical temperature distribution, as is obtained when the sample is directly heated by an alternating current. Figure 10a shows the temperature distribution and Figure 10b the linear changes occurring in such a case.

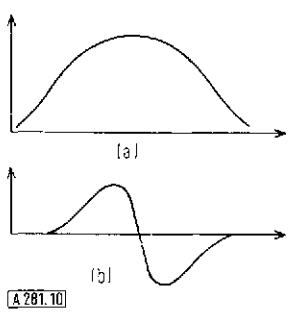

Fig. 10. Temperature distributinn (a) and migration of markers (b) in thermal diffusion through a uniform sample.
Ordinate: (a) Temperature
(b) Variation of distance between a migrating marker and a fixed marker (in an unaltered part of the sample).
Abscissa: Position coordinate.

In the cold regions of the sample, the motion of the markers is immeasurably small; in the middle of the sample, the mobilities of the lattice constituents are at a maximum, but here the driving force disappears (the temperature gradient is zero).

Alloys (as well as pure metals) frequently undergo transformations at higher temperatures: samples which contain only a single phase at room temperature can become multiphased in the presence of a temperature gradient. There are stepwise changes in mobility of the lattice constituents at the phase boundary. The same driving force therefore produces very different effects to the right and left of the phase boundary, and thus there is a jump in the linear change of the sample at the phase boundary (Fig. 11). The relationships represented here correspond to an ideal case in which the disturbance of the thermal equilibrium of the defect distribution by the transport process at every location within the sample remains negligible. This condition does not always hold [58].

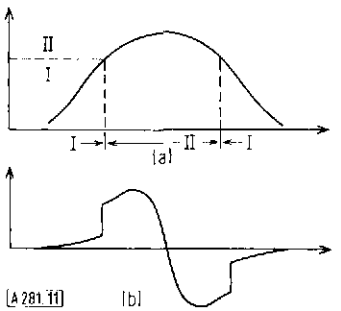

Fig. 11. Temperature distribution (a) and migration of markers (b) in thermal diffusion through a sample consisting of two phases (I and II). For ordinate and abscissa, see caption to Figure 10.

Thermal diffusion causes not only linear but also concentration changes. Figure 12 shows how an originally completely uniform sample of a Cu–Sn alloy containing 29 % by weight of Sn which has a eutectoid structure

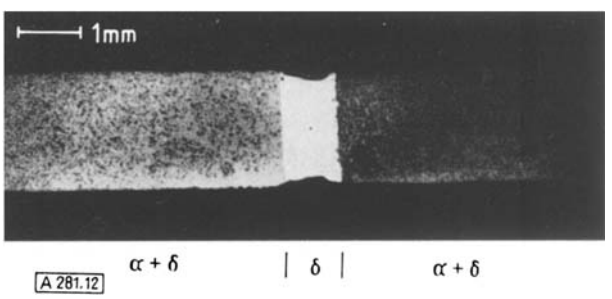

Fig. 12. Change in concentration and dimensions of a Cu–Sn alloy induced by thermal diffusion. Duration of experiment 70 hours; average temperature gradient 300 °C/cm; temperature increases from left to right. Left and right: α- + δ-phase Center: δ-phase.

(α- + δ-phase) changes on anealing in a temperature gradient [58]. After the experiment, a narrow band of pure δ-phase (Cu with 32.55 % by weight of Sn) exists in the region heated at about 570 °C. In this region of the sample there are also dimensional changes in a direction transverse to that of the driving force. These cannot be explained by changes in density, since the density difference between the pure phase and the heterogeneous alloy is small.

To review the whole situation, the relationships for transport of matter in metallic two-component systems can be summarized as follows.

In *isothermal diffusion*, the driving forces acting on the two components are quantitatively equal, but are exerted in opposite directions. They are dependent on the position coordinate and on the time ($\sqrt{t}$-law). If both components have the same mobility, as for example in cyclic interchange, then only changes in concentration, but not in dimension occur.

In *electrolytic transport*, the values of the driving forces acting on both components are different, for they depend

on the scattering cross-section for the conduction electrons and on the effective charge. The forces act in the same direction, if the interaction with the conduction electrons, not the field force, constitutes the greater part of the driving force. The forces are dependent upon the position coordinate only when either the concentration or the temperature varies along the sample. With equal mobility of both components, both dimensional and concentration changes are possible.

In *thermal diffusion*, the driving forces on both components are different in magnitude (they depend on the values of the heats of transport). The forces are orientated in the same or opposite directions, according to the signs of the heats of transport, and depend only on the position coordinate (linear time dependence). With equal mobility of both components, changes in dimension and concentration are both possible.

Practical Significance

Transport processes in metals and alloys are of very diverse practical significance. For example, some metals can be welded to one another at high temperatures by simply pressing them together. Such bonding is based upon material exchange at the contact surfaces. One important application of this process is plating, as employed, for example, in the minting of certain coins: iron is covered with a copper or brass coating. In such plating processes, the different rates of migration of the two components can lead to some unexpected results. Thus, a thin, palladium-plated silver wire becomes hollow after a period of time, because the silver diffuses into the palladium faster than the palladium diffuses into the silver. The same process occurs in a zinc rod covered with a copper layer, and causes the copper layer to crack and the zinc rod to become porous inside. Here again, the zinc migrates faster outwards than the copper migrates inwards. However, Hume-Rothery phases, in particular a γ-Hume-Rothery phase, is formed between the copper and the zinc. This phase has a greater specific volume and thereby causes the cracks [60]. Again, the process of sintering is only possible by mass exchange in the solid phase. Complicated metal parts, which can only be produced with difficulty by machining a cast ingot, are frequently produced nowadays by sintering compressed metal powders.

The migration of matter under the influence of an electric current or a temperature gradient is still so little known and investigated that its practical importance cannot be estimated. However, the wear observed on hard alloy steel chisels has been explained by these phenomena [61].

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[60] *H. Bückle:* Lecture on powder metallurgy at the first Plansee-Seminar, Reutte/Tirol (Austria) 1953.

[61] *Th. Hehenkamp* and *Th. Heumann*, Arch. Eisenhüttenwes. *33*, 510 (1962).

Emulsion Polymerization of Vinyl Monomers under the Influence of Ionizing Radiation

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Ionizing radiation induces the polymerization of some vinyl monomers in aqueous emulsion with high radiation yields. With identical emulsion compositions, the kinetics of this reaction and the kinetics of emulsion polymerization induced by water-soluble initiators are very similar. The rate of reaction in emulsion polymerization is about one hundred times greater than in bulk polymerization. The initiation of emulsion polymerization by means of ionizing radiation permits uniform "illumination" of the reacting volume, as well as almost any desired variation in the frequency of initiation during the reaction. The sharp decrease in the overall rate of reaction when initiation is interrupted during emulsion polymerization of styrene induced by γ-rays contradicts the earlier concept of sharply separated reaction zones.

1. Introduction

Polymerization processes initiated by nuclear radiation have received a great deal of attention in recent years [1–3]. While "classical" catalysts may only induce either radical (peroxy compounds, redox systems) or ionic polymerization (cationic: Lewis acids, hydrogen ions; anionic: Lewis bases, hydroxyl ions), ionizing radiation (chiefly γ-, electron, or X-rays) can initiate both radical and (at low temperatures) ionic poly-

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[1] *R. Roberts:* Review Series No. 13. IAEA, Vienna 1961.

[2] *A. J. Swallow:* Radiation Chemistry of Organic Compounds. Pergamon Press, London 1960.

[3] *A. Chapiro:* Radiation Chemistry of Polymeric Systems. Interscience Publishers, New York, London 1962.

merization processes. This phenomenon may be explained by two competitive processes: radical formation via homolytic decomposition of excited molecules, M**:

$$\underset{\text{Ionization}}{M \rightsquigarrow} \; M^+ + e^- \xrightarrow{\text{Neutralization}} M^{**} \xrightarrow{\text{Homolysis}} R^1\cdot + R^2\cdot$$

and the reaction of positive molecular ions M^+ with neutral monomer molecules, M:

$$M^+ + M \rightarrow MM^+ + M \rightarrow MMM^+ \text{ etc.}$$

Up to the present, only a few examples of anionic polymerization induced by radiation have become known (cf. acrylonitrile [4], hydrogen cyanide [5]); indeed, the mechanism is not yet completely confirmed. In these reactions, the initiators are thermal electrons or negatively charged molecular ions.

The frequency of initiation in radiation-chemical polymerizations is practically independent of temperature. In chemically catalysed processes, on the other hand, the rate of radical formation increases with temperature. In radiation-induced polymerization, the frequency of initiation can be varied almost at will even during the reaction by changing the dose rate.

The average molecular weight of the polymer decreases with increasing dose rate. At extremely high dose rates (impulses from linear accelerators, ca. 10^5 rad/pulse, at a maximum of about 300 discharges/sec) some monomers will cease to polymerize.

The kinetics of radiation-induced radical polymerization in homogeneous systems corresponds to the kinetics of catalytically induced radical polymerization. At low dose rates (low frequency of initiation I), the overall reaction rate v_{Br} is proportional to $I^{1/2}$, since chain termination occurs essentially in a biradical fashion. It is assumed that the system remains homogeneous and that no gel effect (Trommsdorff effect) [5a] is involved (increase of v_{Br} as the viscosity of the system inhibits the combination of radical chain ends).

2. Fundamentals of Emulsion Polymerization

The kinetics of emulsion polymerization differ in many respects from the kinetics of polymerization in a homogeneous medium. Some of the properties of the resulting polymers are also different [6–9].

As far as is known at present, polymerizations in emulsions are induced only by radicals. A polymerizable emulsion is normally [8a] comprised of water, sufficient emulsifier to exceed the critical concentration for micelle formation, a liquid monomer, and a water-soluble initiator or initiating system (*e.g.* a redox system) which yields radicals on decomposition. According to a qualitative theory of emulsion polymerization [9], a portion of the monomer dissolves in the emulsifier micelles, causing the latter to swell (*e.g.* from ca. 35 Å to ca. 45 Å in diameter). A small amount of monomer is in true solution in the aqueous phase, but the greater part is emulsified. The usual recipes contain about 10^{18} micelles/ml, and, depending on the type of emulsifier, the micelles are about 50 Å in diameter, with 50 to 100 monomer molecules per micelle. The concentration of the monomer droplets is about 10^{10}/ml, and their average diameter is about 3 μ. Thus, at the start of a polymerization with an initial monomer: water ratio of 1:5, about one-eighth of the monomer is in micelles, the rest in droplets.

The initiator radicals formed in the aqueous phase impinge principally on the micelles, thus inducing polymerization in the latter. The probability of collision between the radicals on the micelles is highest because of the great number of micelles present. The monomer, which is soluble in the polymer, diffuses out of the droplets, via the aqueous phase, into the polymerizing particles. The diameter of the latter towards the end of polymerization is of the order of magnitude of 10^3 Å; free emulsifier is continually being adsorbed on the increasing surface of the particles. The concentration of emulsifier in the aqueous phase is thus constantly decreasing, and can fall below the critical concentration for micelle formation. If this happens, the formation of new polymer particles practically ceases. Finally, the monomer droplets, too, are consumed [9b], so that polymerization can be sustained only by the monomer dissolved in the latex particles.

The overall rate of reaction, v_{Br}, increases until the free micelles disappear (period I, particle formation), and then remains constant until the monomer droplets are consumed (period II, zero order of reaction). At this point, it decreases to become first order in relation to the concentration of monomer in the monomer-polymer particles (period III).

The quantitative theory developed on this basis [10, 11] involves certain assumptions and simplifications. The radicals are formed in the aqueous phase and penetrate the monomer-polymer particles one at a time. Chain termination can be caused only by a radical which has penetrated this particle, and not by a radical in a neighboring particle, as the particles have completely separate reaction zones. The number of radicals must always be of the same order of magnitude as the number of particles present in the system (in a frequent limiting case, about half of the particles contain a radical). Furthermore, no polymerization can occur outside the particles, *e.g.* in the aqueous phase or in the monomer droplets. These assumptions, no doubt, hold only approximately in many cases. Deviations from the theory are to be expected chiefly with markedly water-soluble monomers [11a] and

[4] *A. D. Abkin, A. P. Sheinker, M. K. Yakovleva,* and *L. P. Mezhirova,* J. Polymer Sci. *53,* 39 (1961); *A. D. Abkin, A. P. Sheinker,* and *L. P. Mezhirova,* Zhur. Fiz. Khim. *33,* 2636 (1959). See however [45].

[5] *D. Hummel* and *O. Janssen,* Z. physik. Chemie N.F. *31,* 111 (1962).

[5a] The gel effect was discovered independently by several authors: *E. Trommsdorff* et al. [12]; *R. G. W. Norrish* and *R. R. Smith,* Nature (London) *150,* 336 (1942).

[6] *H. Gerrens,* Fortschr. Hochpolymeren-Forsch. *1,* 234 (1959).

[7] *H. Fikentscher, H. Gerrens,* and *H. Schuller,* Angew. Chem. *72,* 856 (1960).

[8] *F. A. Bovey, I. M. Kolthoff, A. J. Medalia,* and *E. J. Meehan:* Emulsion Polymerization. Interscience Publishers, New York, London 1955.

[8a] *Vanderhoff* and *McConnell Wiley* [9a] have recently described "inverse" emulsion polymerizations, in which a water-soluble monomer is emulsified in an inert organic phase, and the polymerization is induced with a radical-forming substance or by radiation.

[9] *H. Fikentscher,* Angew. Chem. *51,* 433 (1938); *W. D. Harkins,* J. Amer. chem. Soc. *69,* 1428 (1947).

[9a] Brit. Pat. 884782 (Dec. 20th, 1961), Dow Chem. Comp., inventors: *J. W. Vanderhoff* and *R. McConnell Wiley*; Brit. Pat. 841127 (July 13th, 1960), Dow Chem. Comp., inventors: *J. W. Vanderhoff* and *R. McConnell Wiley.*

[9b] It should be noted that only a small part of the monomer-filled micelles collides with the radicals, unless extremely high concentrations of initiator are used. It could be shown that if a pure monomer phase (droplets) is lacking, the micelles become the suppliers of monomer. The number of latex particles in 1 ml of the fully polymerized emulsion is about one order of magnitude smaller than the original number of micelles per ml of emulsion.

[10] *W. V. Smith* and *R. H. Ewart,* J. chem. Physics *16,* 592 (1948).

[11] *R. N. Haward,* J. Polymer Sci. *4,* 273 (1949).

[11a] *E. Trommsdorff* et al. [12], as well as *N. Sata* and *Y. Harisaki* [13], and others, have discussed the extent of polymerization in the solution particularly at the start of the reaction.

with very large or very small quantities of emulsifier. Moreover, the type of emulsifier has a significant effect on the kinetics of emulsion polymerization. In practice, very good agreement between theory and experiment has been found only in the case of styrene [11b].

3. Kinetics of Emulsion Polymerization Induced by Ionizing Radiation

a) Initiation and Chain Termination

The kinetic relationships in radical chain reactions induced by radiation or light, and in those initiated chemically are usually the same. The differences occur in the initiation and perhaps in chain termination at extremely high dose rates. In radiation-induced emulsion polymerization, the initiating radicals can be formed in all the phases of the system: in the monomer phase, in the aqueous phase, and on the emulsifier molecules; and in addition, as the polymerization proceeds, on the surface of the polymer molecules. The number of radicals formed in each phase is determined by the concentration of molecules (or, more exactly, of their electrons), by their sensitivity against radiation and possibly also by the geometry of the emulsion system (size of droplets and of micelles, average distance between micelles). In addition, it should be noted that by no means all radicals produced by radiolysis are equally effective [14,15]. At low emulsifier concentrations the initiating radicals formed in the emulsifier can be neglected. If the radiation sensitivity of the monomer is significantly smaller than that of water, radicals will be formed predominantly in the aqueous phase. The same must be true for systems with low initial concentrations of monomer.

In water, ionizing radiation mainly causes homolytic cleavage. A highly simplified picture of the reaction would be

$$H_2O \rightsquigarrow H\cdot + OH\cdot$$

In addition, the following process, which yields hydrogen molecules rather than atoms, is considered:

$$2\,H_2O \rightsquigarrow H_2 + 2\,OH\cdot$$

These OH radicals appear to be particularly effective for inducing polymerization. Initiation by OH radicals has been demonstrated for the radiation-chemical polymerization of aqueous solutions of acrylonitrile [16]. Whether, and to what extent, hydrogen atoms are present and induce polymerization, has not yet been clarified [17]. Nothing definite is known about the nature of the radicals which are produced radiolytically in the monomer and then initiate polymerization.

b) Transition to Bulk Polymerization: Dispersion Polymerization and Bead Polymerization

In dispersion polymerization and bead polymerization, no micelle-forming emulsifier is used; instead, a protective colloid, *e.g.* polyvinyl alcohol, is usually employed. In dispersion polymerisation, water-soluble initiators, *e.g.* potassium persulfate, are used, occasionally with addition of a reducing agent such as sodium bisulfite. At very high concentrations of the protective colloid, kinetic similarities to emulsion polymerization become apparent. In bead polymerization, an "oil-soluble" initiator is employed, *e.g.* dibenzoyl peroxide. The kinetics of bead polymerization correspond to the kinetics of bulk polymerization (*i.e.* the reaction becomes a "water-cooled bulk polymerization"); the rate of polymerization in the region of low conversions is proportional to the square root of the initiator concentration (chain termination by combination of free radicals at chain ends).

The kinetics of polymerization are more complicated. The initiating radicals originate in the aqueous phase and penetrate into the monomer droplets, but they can also cause polymerization of dissolved monomer molecules in the aqueous phase. Depending on the size distribution of the dispersed droplets (which is a function of the type and concentration of the protective colloid) and on the solubility of the monomer in water and in the polymer, the reaction may resemble either emulsion polymerization having a high reaction rate and forming high molecular weight products, or bead polymerization, possibly with a certain amount of precipitation polymerization. In precipitation polymerization the particles of polymer precipitate from the solution when they exceed a limiting size.

If a dispersion polymerization is induced by radiation, additional initiating radicals can be generated within the protective colloid and within the monomer droplets. The kinetics then become even more complicated. The only thorough study on this subject is the work of *Chapiro* and *Maeda* [18]. Their polymerization recipe comprised 5.5 ml of styrene, 0.09 g of polyvinyl alcohol, and 45 ml of water. Polymerization was effected in the absence of air in sealed, agitated Pyrex glass vessels, using radiation from a 200 curie ^{60}Co source. The most important findings and some values for comparison are given in Table 1. Up to about 60 %, the conversion was linear with time. The gradient of the straight part of the curve was approximately proportional to the 0.65th power of the dose rate:

$$v_{Br} \sim I^{0,65}$$

(v_{Br} = overall rate, I = frequency of initiation $\sim$ dose rate.)

The power of I is somewhat higher than that observed in bulk polymerization (0.5) or in emulsion (0.4 for styrene). Higher powers of I (between 0.5 and 1.0) are found chiefly in precipitation polymerization [22], where the polymer precipitates from solution as soon as it has reached a certain size. The occluded radical end of the precipitated polymer is still accessible for monomer molecules, but can hardly combine with other growing

[11b] A summary of the assumptions of the quantitative theory of emulsion polymerization may be found in [7], p. 858.

[12] *E. Trommsdorff, H. Köhle*, and *P. Lagally*, Makromolekulare Chem. *1*, 169 (1947).

[13] *N. Sata* and *Y. Harisaki*, Kolloid-Z. *124*, 36 (1951).

[14] *C. H. Bamford* and *A. D. Jenkins*, J. Polymer Sci. *53*, 149 (1961).

[15] *S. Okamura, K. Katagiri* and *T. Yonezawa*, J. Polymer Sci. *42*, 535 (1960).

[16] *F. S. Dainton*, J. physic. Colloid Chem. *52*, 490 (1948).

[17] *E. Collinson* and *F. S. Dainton*, Discuss. Faraday Soc. *12*, 212 (1952); *F. Fiquet* and *A. Bernas*, J. Chim. physique Physico-Chim. biol. *51*, 47 (1954).

[18] *A. Chapiro* and *N. Maeda*, J. Chim. physique Physico-Chim. biol. *56*, 230 (1959).

Table 1. Dispersion polymerization of styrene at 20 °C [18].
Styrene: water ratio = 1:10; 0.18 % polyvinyl alcohol as protective colloid.

Dose rate [a] [eV/g/min]	v_{Br} [%/min]	v_{Br} for bulk polymn. [b] [%/min]	Dose [eV/g]	$\overline{MW}$ of soluble fraction	$\overline{MW}$ in bulk polymn. [c]	Insoluble in benzene [%]
8.7×10^{15}	0.007	0.0014 to 0.0017	2.62×10^{19}	16100	150000	17.1
			1.45×10^{19}	22800		20.9
2.21×10^{15}	0.0032	0.00075	3.78×10^{19}	23600	280000	12.8
			2.44×10^{19}	27200		13.8
			1.28×10^{19}	34700		16.6
0.97×10^{15}	0.0017	0.0005	1.74×10^{19}	55000	410000	22.1
			1.48×10^{19}	43000		20.3
			1.05×10^{19}	51000		25.3

v_{Br} = overall rate of reaction; $\overline{MW}$ = average molecular weight.
[a] *Chapiro* [3] gives values about 7 % lower.
[b] From [19] and [20].
[c] From [20].
[d] In order to obtain the same conversion rate, *Ballantine* et al. [21] required 20 times the dose rate (1.78×10^{17} eV/g/min) in bulk polymerization at 30 °C.

chains. Because of the low solubility of styrene in water, the extent of solution polymerization is obviously small.

The average molecular weights of the soluble portions were inversely proportional to the square root of the dose rate:

$$\overline{MW} \sim I^{-0.5}$$

This is the relationship found for polymerizations in homogeneous medium involving biradical chain termination.

The overall rate of reaction v_{Br} was three to five times greater than that in radiation-induced bulk polymerization of styrene [22a]. This can be explained either by a greater frequency of initiation (if the rules of homogeneous polymerization apply) or by a retarded termination reaction. The latter is improbable, since the Trommsdorff effect in styrene should appear only at higher conversions (however, see [23]). Moreover, because of the low concentration of protective colloid [23a] (large particles) and because of the low molecular weights, comparison with emulsion polymerization is not possible. We assume that the OH radicals formed in the aqueous phase (and perhaps the H atoms) play a significant role in initiation. The frequency of initiation here is twenty to thirty times greater than that in radiation-chemical bulk polymerization of styrene. It is also assumed in this connection that the "kinetic chain length" in dispersion polymerization of styrene induced by γ-rays is only about half as great as that in the bulk polymerization (half the average molecular weight at the same overall reaction rate), but v_{Br} is three to five times as large. The total irradiated volume in these experiments was about nine times as great as the volume of monomer; the total number of polymer chains created is therefore only 2.5 to six times as great as in the bulk polymerization of styrene. In the dispersion polymerization of styrene, $G_{polymer}$ [23b] is 2 4 ($G_{R,\,styrene} = 0.6$–0.7 [24]). The agreement with G_{OH} (≈ 2.6) does not necessarily imply that a considerable portion of the radicals formed in water have induced polymerization, since both the extent of transfer reactions and the G_R value for styrene are not known exactly. *Ballantine* et al. [21] give about 2 at 25 °C, while *Okamura* et al. [25] give $G_{R,\,styrene} = 1.7$. If these values are correct, then during dispersion polymerization of styrene induced by γ-radiation, only a small amount of initiation takes place in the aqueous phase.

Very peculiar features of the reaction were the formation of a considerable proportion (13–25 %) of benzene-insoluble material, the decrease in the amount of this gel at increasing conversion, and its high proportion at low dose rates. This effect is undoubtedly the result of a side reaction. Crosslinking of polystyrene to this extent by doses of the order of 10^5 rad is out of the question.

Chapiro and *Maeda* propose that the benzene-insoluble material is a graft polymer of styrene and polyvinyl alcohol. The fact that the amount of benzene-insoluble material decreases with increasing conversion may then be explained as follows: in aqueous solution (at a concentration of several percent), polyvinyl alcohol depolymerizes rapidly on irradiation; the first molecular weight minimum is reached at about 2×10^5 rad [26]. Evidently these radical fragments initiate block polymerization. The copolymers are initially hydrophilic and insoluble in benzene, and hence remain in the aqueous phase or in the boundary layer. If the polyvinyl alcohol chain in the copolymer is degraded, presumably with further grafting, the fraction of polystyrene finally becomes so large that the copolymer becomes soluble in benzene. One can also visualize transfer processes from the growing polymer chains to the polyvinyl alcohol with subsequent grafting.

[19] *M. Magat* and *L. Reinisch*, Int. J. appl. Radiat. Isotopes *1*, 194 (1956).

[20] *A. Chapiro* and *P. Wahl*, C. R. hebd. Séances Acad. Sci. *238*, 1803 (1954).

[21] *D. S. Ballantine, A. Glines, D. D. Metz, J. Behr, R. B. Mesrobian*, and *A. J. Restaino*, J. Polymer Sci. *19*, 219 (1956).

[22] *A. Chapiro, C. Cousin, Y. Landler*, and *M. Magat*, Recueil Trav. chim. Pays-Bas *68*, 1037 (1949).

[22a] The data for the overall rate of reaction in radiation-induced bulk polymerization of styrene vary considerably, so that the ratio given here seems uncertain.

[23] *B. M. E. van der Hoff*, J. Polymer Sci. *33*, 487 (1958).

[23a] Normal industrial suspension polymerizations employ 5–10% protective colloid, based on the monomer.

[23b] G-value = number of polymer molecules formed per 100 eV of absorbed radiation energy.

[24] *A. Chapiro* and *M. Magat:* Actions Chimiques et Radiobiologiques des Radiations. 3e série, Masson, Paris 1958.

[25] *S. Okamura, T. Manabe*, and *S. Futami*, J. chem. Soc. Japan, ind. Chem. Sect. *60*, 853 (1957); Chem. Zbl. *1959*, 2408.

[26] *K. Shinohara, A. Amemiya, M. Matsumoto, Y. Shinohara*, and *S. Ohnishi:* Peaceful Uses of Atomic Energy II. Genf 1958, Vol. *29*, p. 186.

c) Emulsion Polymerization of Styrene

The first quantitative investigation of radiation-induced polymerization of styrene was carried out by *Ballantine* et al. [27]. Their most important findings and the values of other authors are summarized in Table 2. *Ballantine* et al. found the reaction rates to increase with rising temperatures (this was not supported by *Meshirova* et al. [28] and *Hummel* et al. [30]). Log v_{Br} was a linear function of the reciprocal of the temperature, from which the total activation energy of the reaction (E_{Br}) was found to be 3.69 kcal/mole. This overall energy is the sum of the activation energy of the propagation reaction (E_W) and the apparent activation energy of particle formation (E_N):

$$E_{Br} = E_W + E_N$$

E_W is certainly larger (*Vanderhoff* et al. [29] give 7.2 kcal/mole; *Smith* [31] gives 11.7 kcal/mole) than E_{Br}; hence E_N is negative.

Meshirova et al. [28] followed the reaction by dilatometry; because of the high dose rate, periods I and II could not be differentiated. Neither the overall reaction rate nor the average molecular weight showed any distinct dependence on temperature, as *Ballantine* et al. observed. From the overall rate of reaction and the average degree of polymerization, *Meshirova* et al. estimated the termination constant k_t to be of the order of 10^1 to 10^3. If the radiation source was removed during the polymerization, the reaction continued for some time longer (see Tables 2 and 3).

Table 2. Radiation-initiated emulsion polymerization of styrene. Radiation source: ^{60}Co; in [27], ^{182}Ta).

Dose rate [*] [eV/g/min]	Temp. [°C]	Emulsifier [% based on H_2O]	Styrene: water ratio	v_{Br} [%/min]	$\overline{MW}$ of polymer $\times 10^{-6}$	Ref.
0.5×10^{14}	25	1.3 % Na-dodecyl sulfate	ca. 1:8	0.18 (max.)	3.5	[30]
2×10^{14}				0.36 (max.)	2.7	
	30	1.5 % Na-2.25 % dihexyl-2.25 % sulfosuccinate	1:4	–	0.821	[29]
			1:1.5		1.04	
					1.25	
5.03×10^{16}	50	1.5 % Na-2.25 % dihexyl-2.25 % sulfosuccinate	1:4	–	1.15	
			1:1.5		1.54	
					1.92	
	70	1.5 % Na-2.25 % dihexyl-2.25 % sulfosuccinate	1:4	–	1.39	
			1:1.5		1.99	
					2.34	
6.06×10^{16}	25	1 % "Duponol G" [**]	1:9	0.6	1.726 (start) 0.885 (end)	[27]
	35			0.75	1.5 (start) 0.8 (end)	
	45			0.9	2.06 (start) 1.2 (end)	
2.5×10^{17}	25–87	3 % $C_{15}H_{31}SO_3Na$	1:3	6.65 (50 °C)	1.72–1.56	[28]
	50–87	3 % $C_{17}H_{33}COONa$		12.4 (50 °C) (start)	1.53–1.04	

v_{Br} = overall reaction rate; $\overline{MW}$ = average molecular weight.
[*] The values given in rad/hr have been recalculated to eV/g/min, taking the density of the media into account.
[**] Probably an amine salt of an *n*-alkyl sulfate.

According to the theory of emulsion polymerization, the overall rate of reaction increases with the 0.4th power of the initiation frequency. The values found by *Meshirova* et al. [28] and by ourselves [30] for the overall rate of reaction follow this dependence with surprising exactness. The values of *Ballantine* et al. [27] lie markedly lower, possibly because the authors did not take into account the inhibition period and the influence of oxygen which diffused in. Fig. 1 shows the decrease in the average molecular weight as the reaction proceeds.

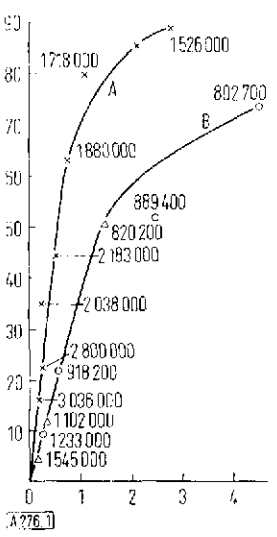


Fig. 1. Decrease in average molecular weight (values adjoining experimental points) with progressive emulsion polymerization of styrene [25]. Reaction temperature: 25 ± 1.5 °C; initial polymerization rate: 0.60 %/min; radiation source: ^{182}Ta; dose rate: 60000 rad/hr.
Curve A: Styrene: water ratio 1:7. Emulsifier: 3 % Duponol G.
Curve B: Styrene: soap solution ratio 1:9. Emulsifier: 1 % Duponol G.
O and Δ: Values from two series of experiments.
Ordinate: Conversion [%]. Abscissa: Time [hrs].

[27] *D. S. Ballantine, A. Glines, T. Colombo*, and *E. Manowitz*, U.S.-Atomic Energy Commission BNL Report 294, March 1954.

[28] *L. P. Meshirova, M. K. Yakovleva, A. V. Matvejeva, A. D. Abkin, P. M. Chomikorsky*, and *S. S. Medvedev*, Vyssokomolek. Ssoedineniya *1*, 68 (1959).

[29] *J. W. Vanderhoff, E. B. Bradford, H. L. Tarkowski*, and *B. W. Wilkinson*, J. Polymer Sci. *50*, 265 (1961).

[30] *D. Hummel, G. Ley*, and *Christel Schneider*, presented at the ACS-Meeting, Chicago 1961; Advances Chem. Series *34*, 60 (1962).

[31] *W. V. Smith*, J. Amer. chem. Soc. *70*, 3695 (1948).

[31a] *J. W. Vanderhoff*, personal communication.

Vanderhoff et al. [29] investigated the emulsion polymerization of styrene induced by γ-rays using the method of competitive particle growth: monomer is added to a monodisperse latex containing particles of two sizes, and polymerization is initiated catalytically or with ionizing radiation (dose rate 3.3×10^5 rad/hr; polymerization time 12 to 18 hours [31a]). The rate of volume increase is proportional to the nth power of the particle diameter:

$$dV/dt \sim D^n$$

The theory of emulsion polymerization of *Smith* and *Ewart* [10] requires that n be zero (particle growth independent of particle volume). *Vanderhoff* et al. found similar or identical values of n (n = 1–2 for small particles) in emulsion polymerization initiated either by persulfate or by γ-radiation. When using the oil-soluble initiator dibenzoyl peroxide and sufficiently large latex particles (2640 Å and 5570 Å), n was 3; with smaller latex particles, polymerization could no longer be induced by benzoyl peroxide. These results show that emulsion polymerization of styrene proceeds similarly whether it be initiated by $K_2S_2O_8$ or by γ-radiation, which would cause formation of initiating radicals predominantly in the aqueous phase. The Smith-Ewart kinetics are not followed rigorously.

Table 3. Reaction constants for emulsion and bulk polymerization of styrene.

	Bulk polymn. [32]	Emulsion polymerization				
		[31]	[23]	[29]	[28]	[30]
Monomer:water ratio	–	–	1:8	1:4 1:1.5	1:3	1:7
Emulsifier	–	"soap"	"soap"	1.5 % Na-dihexyl-sulfosuccinate	3 % $C_{15}H_{31}SO_3Na$ or $C_{11}H_{23}CO_2Na$	1.3 % Na-dodecyl-sulfate
Temp. [°C]	30	25 50	50	30	25 to 27	25
Diameter of polymer particles [Å]	–	500 1500 [a]	2210	680–1320 940–1850	–	880–1440
k_p/k_t [*]	2.178×10^6 [b]	–	–	–	–	0.089
k_p [l/mole/sec]	55	110 [c] 390	122	88–160	–	–
k_t [l/mole/sec]	2.525×10^7 [b]	–	3.1×10^4	5.25×10^3 [d]	$10-10^3$	1.32×10^3 [e]

[*] k_p = propagation constant; k_t = termination constant.
[a] Average diameter.
[b] Chain termination by radical combination. In the original publication, the values are given for $k_p/2\,k_t$ ($= 1.089\times10^6$) and for $2\,k_t$ ($= 5.05\times10^7$).
[c] Activation energy of the propagation reaction E_p = 11.7 kcal/mole.
[d] Calculated on the assumption that all radicals formed in the aqueous phase can initiate polymerization.
[e] Calculated from k_p/k_t with k_p = 110 [31].

The ability of the polymer particles to absorb monomer was determined using fully polymerized latices (see Table 2, [29]). The ratio of monomer concentration to that of polymer increased linearly with particle diameter and lay between 1.3 and 2.2. From this result, values were obtained for the monomer concentrations occuring in the monomer/polymer particles during polymerization.

An interesting result was obtained in the calculation of ρ (rate of entry and formation of radicals in the particles) from the G_R values [32a] for the different types of molecules present in the reactions (the emulsifier was not considered). Table 4 shows that in emulsions containing 20 % styrene, 98 % of the radicals are formed in the aqueous phase; even in emulsions with 40 % styrene, the figure is still 95.8 %. Even if the value of G_R for water should be too large (according to *Hochanadel* $G_R(H^\bullet) + G_R(OH^\bullet) = 4.8$, cf. [2]), it is safe to say that in emulsion polymerization induced by γ-irradiation the majority of radicals is formed in the aqueous phase.

Table 4. Radical formation in radiation-initiated emulsion polymerization of styrene

Phase	G_R [radicals per 100 eV of absorbed radiation energy]	20 % styrene			40 % styrene	
		Radicals formed per sec and g of phase [*]	% of total radical production	ρ [radicals per sec and g of MP particles]	% of total radical production	ρ [radicals per sec and g of MP particles]
Water	6.7	5.6×10^{13}	98 %		95.8 %	
Styrene	0.7	3.5×10^{12}	1.5 %	23×10^{13}	4.0 %	8.8×10^{13}
Polystyrene	0.1	3.4×10^{11}	0.5 %		0.2 %	

[*] At a dosage rate of 48400 rad/hr or 5.05×10^{16} eV/min per g of H_2O.
MP particles = monomer-polymer particles.

[32] *M. S. Matheson, E. E. Auer, E. B. Bevilacqua*, and *E. J. Hart*, J. Amer. chem. Soc. *73*, 1700 (1951).

[32a] The value of G_R for water has been determined to be 6.7; this value includes the formation of H atoms.

We followed the emulsion polymerization of styrene induced by γ-rays by using a dilatometer (see Tables 2 and 3) [30]. The apparatus (Fig. 2) is similar to that described by *Gerrens*.

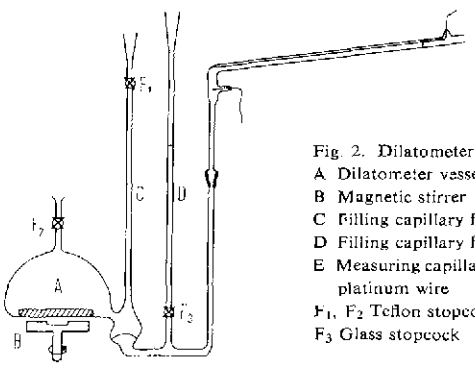
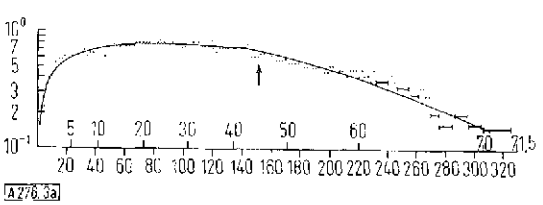


Fig. 2. Dilatometer
A Dilatometer vessel
B Magnetic stirrer
C Filling capillary for emulsion
D Filling capillary for mercury
E Measuring capillary with platinum wire
F_1, F_2 Teflon stopcocks
F_3 Glass stopcock

A 276.2

A precision capillary (selectively 2, 3, or 4 mm in diameter) was used for measurement. It was filled with mercury and had a platinum wire of 0.1 mm diameter sealed in axially. As the emulsion contracts during polymerization, it pulls the mercury column along with it and gradually frees the platinum filament; the change in resistance is indicated on a compensating recorder. Before each measurement, the capillary must be cleaned with a chromic acid/sulfuric acid mixture. The apparatus was placed in a thermostat in such a way that the reaction vessel stood above a submerged magnetic stirrer. The system was fixed in the radiation zone with geometric reproducibility. The homogenized emulsion was introduced under argon.

The radiation source was a ^{60}Co cylinder with an activity of 6 to 7 curies. The dose rates amounted to 200, 50, or 22 rad/hr (or 2.0×10^{14}, 0.5×10^{14}, or 0.22×10^{14} eV/g/min) depending on the geometric arrangement. The inhibition period lasted 1 to 150 minutes, usually about 10 minutes. To stop the reaction, the radiation source was lowered into a concrete shield, and the latex poured into a solution of hydroquinone. Figure 3a shows the course of reaction with styrene. It corresponds closely to the curve obtained with $K_2S_2O_8$ as initiator.



A 276.3a

Fig. 3a. Emulsion polymerization of styrene.
↑: disappearance of pure monomer phase.
Ordinate: logarithm of the overall rate of reaction [mg of polymer formed per g of emulsion every 2 min]
Abscissa: top: conversion [%]
bottom: time [min]

Theory requires that, after the conclusion of particle formation and in the presence of monomer droplets, the overall rate of reaction v_{Br} be independent of the frequency of initiation. To test this for emulsion polymerization induced by γ-rays, the dose rate was raised from 50 rad/hr to 200 rad/hr during the period of zero order reaction. The overall rate of reaction rose by about 30 %. This can probably be explained by assuming that the average radical concentration per particle is increased somewhat (> 0.5), so that the termination reaction is retarded to some extent (Trommsdorff effect). This agrees qualitatively with the finding of *Vanderhoff* [23]. If the polymerization is carried out with a fourfold dose rate (frequency of initiation) right from the start, then the maximum overall rate of reaction (period of zero order) is doubled, corresponding to the relationship

$$v_{Br} \sim I^{0.5}$$

Theory requires a function of the 0.4th power. It is not yet possible to say whether the difference observed is real.

We determined the relationship between the growth constant k_p and the termination constant k_t from the pre- and after-effect (see Section 4). Using the value of k_p for emulsion polymerization of styrene at 25 °C, the constant for the termination reaction, k_t, is found to be 1320 l/mole/sec. *Vanderhoff* et al.[29] calculated a value of 5250 from their experiments. The difference between the two values is not excessive in view of the experimental uncertainty inherent in both methods; both values, nevertheless, lie about four orders of magnitude below that for bulk polymerization of styrene ($2k_t = 5.05\times10^7$ [32]). Thus, the retardation of the termination reaction in emulsion polymerization of styrene required by the theory is proven.

The value of ρ calculated from our results amounts to 1.2×10^{13} radicals/min per gram of emulsion (using the high value of G_R for water, 6.7, and neglecting the organic phase). During the period of zero order reaction, about 9×10^{13} molecules of polymer are formed per minute. This seems to indicate that each radical generates seven to eight polymer molecules. This surprising result is attributable in part to transfer reactions (see Section 3 g δ).

d) Methyl Methacrylate

Styrene is soluble in water at 25 °C to the extent of 0.027 % [8], methyl methacrylate at 20 °C to the extent of 1.6 %. Hence, the reaction in the aqueous phase can no longer be neglected in emulsion polymerization of methyl methacrylate, as it was in the case of styrene [12]. During polymerization, the polymer particles formed in the aqueous phase become normal monomer-polymer particles in the presence of an emulsifier, by uptake of monomer. As a consequence, there is a steep rise in the overall rate of reaction in period I. In addition, the gel effect comes into play sooner and more strongly than it does with styrene. This is true of bulk as well as of emulsion polymerization.

Okamura et al. [33] determined the overall rate of reaction for bulk polymerization of methyl methacrylate induced by γ-rays, and found that it is constant up to a conversion of 7–8 %, but then increases linearly with the logarithm of the conversion (measurements up to 60 % conversion). It is to be expected that during emulsion polymerisation the overall rate of reaction depends on a higher power of the initiation frequency than theory requires (0.4), owing to the influence of these two effects (particle formation in the aqueous phase and gel effect).

[33] *S. Okamura, H. Inagaki*, and *K. Katagiri*, J. chem. Soc. Japan, ind. Chem. Sect. *60*, 850 (1957); Chem. Zbl. *1959*, 2408.

The influence of the type and concentration of emulsifier on the emulsion polymerization of methyl methacrylate [34] and other monomers [35, 36] in relation to the water-solubility of each monomer has been investigated by *Okamura* and *Motoyama*. For less water-soluble monomers (styrene, methyl methacrylate), they observed a constant increase in the maximum overall rate of reaction with increasing emulsifier concentration, whereas with more water-soluble monomers (methyl acrylate, vinyl acetate, acrylonitrile), the maximum overall rate of reaction decreased again above a certain emulsifier concentration.

Three studies were made on emulsion polymerization of methyl methacrylate initiated by γ-rays [26, 30, 37] (see Table 5). Because of differences in the experimental conditions, the values for the overall rates of reaction cannot be directly compared. The overall rate of reaction for emulsion polymerization of methyl methacrylate induced by γ-radiation is 100–200 times larger than that in bulk polymerization induced by γ-radiation [28, 36, 37]. The values found by *Meshirova* et al. and by ourselves are in good agreement. An overall rate of reaction of about 11 %/min can be calculated for a high dose rate from the value measured at the low dose rate; *Meshirova* et al. found 13.8 %/min (see Table 5).

Table 5. Polymerization of methyl methacrylate.

Bulk polymerization				Emulsion polymerization					
v_{Br} [a] [%/min]	Temp. [°C]	Initiation by	Ref.	v_{Br} [%/min]	Temp. [°C]	Monomer: water ratio	Emulsifier	Initiation by	Ref.
0.09	60	0.1 % benzoyl peroxide	[12]	2.5	70–74	1:5 1:5	0.2 % Turkey red oil	0.0125 % $K_2S_2O_8$	[12]
0.026	30	3×10^{16} eV/g/min	[33]	1.1 [b]	60	1:12.5	0.2 % Na dodecyl sulfate	0.1 % $(NH_4)_2S_2O_8$	[35]
0.057	30	ca. 4×10^{16} eV/g/min	[21]	0.63 [c]	25	1:8	1.3 % Na dodecyl sulfate	2×10^{14} eV/g/min	[30]
				0.9 2.0 4.6	20	not given	0.01 % Na dodecyl 1.0 benzene- 1.0 sulfonate	2×10^{16} eV/g/min	[37]
				0.16 [d] 0.25 0.65	20	1:9	0.1 % lauryltrimethylammonium chloride	2.5×10^{14} 1.5×10^{15} 2×10^{16} eV/g./min	[37]
				13.8 13.8 (start)	25 50	1:3	3 % $C_{15}H_{31}SO_3Na$	2.5×10^{17} eV/g/min	[28]

[a] At low conversions.
[b] Average for first hour.
[c] During the short period of zero order.
[d] Approximate values from a graph; these presumably include the inhibition period and the period of particle formation.

Figure 3b shows a conversion curve determined by us [30]. After a steep rise in the overall rate of reaction during the period of particle formation, there follows a short period of zero reaction order. The curve then rises further and attains a maximum at about 50 % conversion. Shortly thereafter it drops sharply, following neither first nor second order kinetics with respect to

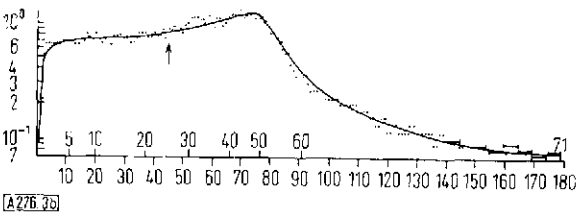


Fig. 3b. Emulsion polymerization of methyl methacrylate.
↑: disappearance of pure monomer phase.
Ordinate: logarithm of the overall rate of reaction [mg of polymer formed per g of emulsion per min]
Abscissa: top: conversion [%]
bottom: time [min]

the monomer concentration in the particles. The very steep rise during period I can be explained by particle formation in the aqueous phase. The overall rate of reaction remains constant for a short time; monomer diffuses via the aqueous phase into the monomer-polymer particles, and the monomer concentration in these remains constant. Since the latex particles can take up monomer to the extent of three to four times the weight of polymer (in the case of styrene, 1.5–2.0 times the weight), the monomer droplets (pure monomer phase) disappear at about 30 % conversion. Now the gel effect in the particles raises the overall rate of reaction considerably; during this period, the major part of the monomer contained in the monomer-polymer particles is consumed. Ultimately, the high viscosity in the particles at high conversions hinders diffusion of monomer; at the same time, the polymerization in the aqueous phase has sunk to a very small value, causing a steep decline in the overall rate of reaction.

No investigations of the influence of changing initiation frequencies during the emulsion polymerization of methyl methacrylate on the overall rate of reaction have yet been made. *Okamura* et al. [37] initiated the emulsion polymeri-

[34] *S. Okamura* and *T. Motoyama*, Chem. High Polymers (Tokyo) *12*, 109 (1955); Chem. Abstr. *51*, 1645 (1957).

[35] *S. Okamura* and *T. Motoyama*, J. chem. Soc. Japan, ind. Chem. Sect. *57*, 930 (1954); Chem. Abstr. *50*, 850 (1956).

[36] *S. Okamura* and *T. Motoyama*, Mem. Fac. Engng. Kyoto Univ. *17*, 220 (1955); Chem. Abstr. *50*, 6831 (1956).

[37] *S. Okamura*, *T. Motoyama*, *T. Manabe*, and *H. Inagaki*, IAEA: Conf. on Large Radiation Sources in Industry, Warsaw 1959, Vol. 1, p. 361.

zation right from the start with various dose rates between 2.5×10^{14} and 2.0×10^{16} eV/g/min, and found that the overall rate of reaction was a function of $I^{0.25}$. This unusually low value is difficult to understand, if no diffusion of radicals out of the particles is assumed, and is probably attributable to partial inhibition by oxygen introduced during sampling.

e) Ethyl Acrylate

We have investigated dilatometrically emulsion polymerization of ethyl acrylate at 25 °C induced by γ-rays at a dose rate of 2×10^{14} eV/g/min. The monomer:water ratio was about 1:7. The average molecular weight of the polymer at the end of polymerization was about 1.6×10^6. Figure 4 shows a plot of the logarithm of the overall rate of reaction versus the reaction time. The curve

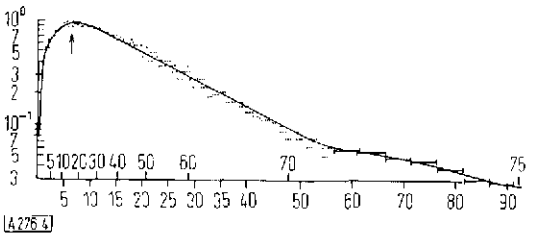


Fig. 4. Emulsion polymerisation of ethyl acrylate.
^: disappearance of pure monomer phase.
Ordinate: logarithm of the overall rate of reaction
[mg of polymer formed per g of emulsion every 15 sec]
Abscissa: top: conversion [%]
bottom: time [min]

reaches a maximum 6.5 minutes after the start of the reaction and then, without undergoing a period of zero order, falls slowly according to first order kinetics relative to the monomer concentration. Beyond about 70 % conversion, the decline becomes slower. The very steep rise in the overall rate of reaction at the beginning of the reaction, in comparison with the polymerization of styrene, is again - at least in part - attributable to the appreciable solubility in water of the monomer (1.8 % at 30 °C). The lack of a period of zero order and the linear decline in log v_{Br} after the maximum might be explained by the absence of a strong gel effect. Experimental data resulting from variation of the initiation frequency during polymerization to test this assumption are not yet available. Also, the solubility of the monomer in the latex particles is unknown. Strangely, the curve for log v_{Br} for methyl acrylate, which has a very strong gel effect, is similar at low emulsifier concentration (see below).

f) Vinyl Acetate

Allen et al. [38,39] reported on emulsion polymerization of vinyl acetate induced by γ-rays in connection with grafting experiments. The monomer:water ratio was generally 1:8, the emulsifier (sodium dioctylsulfosuccinate) concentration was 3.75 % based on the water, and the dose rate was about 6×10^{16} eV/min per gram of emulsion. Under these conditions, the overall rate of reaction at 20 °C in the range of medium conversion amounted to 4 %/min; $G_{monomer}$ can therefore be calculated to be −94 500. This agrees with the very high overall rate observed in catalytically induced emulsion polymerization of vinyl acetate. The molecular weight of the highly branched polymer was of the order of 10^6.

The reaction was extremely sensitive to oxygen; monomer and emulsifier solution were thoroughly degassed beforehand.

g) Transition to Precipitation Polymerization: Methyl Acrylate

As the solubility in water of the monomers increases, their behavior in emulsion polymerization deviates more and more from the "classical" behavior of styrene. Methyl methacrylate still has a short period of zero order, but ethyl acrylate does not. Methyl acrylate is 5 % soluble in water at 30 °C; hence it cannot be expected that the kinetics of emulsion polymerization of methyl acrylate will still conform to theory. We have investigated the effect on the function (log v_{Br})/t of varying recipes, initiation frequencies (dose rates), and temperatures[30].

α) Effect of Initiation Frequency

Figure 5 shows the function (log v_{Br})/t for three identical mixtures, which were polymerized right from the start with dose rates of 200, 50, and 22 rad/hr, respectively. The overall rate of reaction rises to a

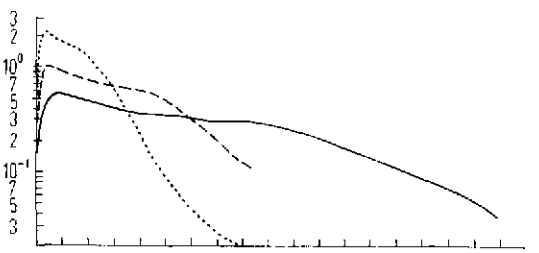


Fig. 5. Effect of the initiation frequency on emulsion polymerization of methyl acrylate.
(1.3 mole of methyl acrylate/kg of emulsion; 45 mmoles of Na lauryl sulfate/kg of solution)
..... 2×10^{14} eV/min/g
– – – – 0.5×10^{14} eV/min/g
——— 0.22×10^{14} eV/min/g
Ordinate: Logarithm of the overall rate of reaction
[mg of polymer formed per g of emulsion every 30 sec]
Abscissa: Time [min]

maximum value within a few minutes (period I). It then falls off (periods II and III), slowly at first and then more rapidly; in periods II and III, the decrease in log v_{Br} is linear to a first approximation. A plot of log $v_{Br,\,max}$ against log I yields a straight line with a slope of 0.55:

$$v_{Br,\,max} \sim I^{0.55}$$

Any increase in the dose rate always led to an increase in the overall rate of reaction, which was approximately proportional to the square root of the dose rate.

[38] *P. E. M. Allen, J. M. Downer, G. W. Hastings, H. W. Melville, P. Molyneux*, and *J. R. Urwin*, Nature (London) *177*, 910 (1956).

[39] *P. E. M. Allen, G. M. Burnett, J. M. Downer*, and *H. Melville*, Makromolekulare Chem. *38*, 72 (1960).

This behavior may be explained as the combined action of two effects (both of which retard the termination reaction): polymerization in solution and hindrance of diffusion of the macro radicals (gel effect). The latter becomes significant already in the region of maximum reaction rate and during period II.

The influence of the solubility in water of monomers on the overall rate of reaction in catalytically initiated emulsion polymerization has been studied recently, in particular by *Okamura* and *Motoyama* [36,40]; their results with methyl acrylate are in qualitative agreement with our own. Dependence of the overall rate of reaction on approximately the square root of the initiation frequency always holds, according to the expanded theory of emulsion polymerization of *Gerrens* [6] (further literature references are given in his article), whenever the gel effect is involved. The extent to which the effects are involved in periods I and II remains unclarified.

Table 6 shows the results of some measurements on dispersions and polymers obtained in emulsion polymerization of methyl acrylate induced by γ-radiation.

Table 6. Effect of the initiation frequency on emulsion polymerization of methyl acrylate at 25 °C. Emulsifier: 1.3 % Na dodecyl sulfate; monomer: water ratio ca. 1:8.

Dose rate [eV/g/min]	$v_{Br,\,max}$ [mg of polymer/min/g of emulsion]	Polymer particles/g of emulsion	Average molecular weight
2×10^{14}	4.4	1.85×10^{14}	1.38×10^{6}
0.5×10^{14}	2.2	1.55×10^{14}	1.62×10^{6}
0.22×10^{14}	1.2	1.27×10^{14}	1.88×10^{6}

$v_{Br,\,max}$ = maximum overall rate of reaction.

The number of particles, determined by ultramicroscopy, increases with the dose rate but apparently somewhat more slowly at higher dose rates. At the same time, the average molecular weight decreases, once again somewhat more slowly at higher dose rates. These results are to some extent in contradiction to the finding of *Gerrens* [41] that the number of particles N and the degree of polymerization $\bar{P}$ are almost independent of the initiator concentration. His results can be partly explained as follows. At the appreciably higher initiation frequencies he used, the free monomer phase soon disappears, and initiation in the aqueous phase can no longer occur to any significant extent. However, this interpretation is still unsatisfactory.

β) Influence of the Emulsifier Concentration and the Monomer:Water Ratio

The experiments were carried out at 25 °C with a dose rate of 0.5×10^{14} eV/min per gram of emulsion (50 rad/hr) and a monomer:water ratio of about 1:7. The concentration of emulsifier (sodium lauryl sulfate) was varied between 7.7 and 11.9 mmoles/kg (0.22–3.44 %). Figure 6 shows the function (log v_{Br})/t for three emulsions. The dashed curve (0.2 % sodium lauryl sulfate) strongly resembles that for emulsion polymerization of ethyl acrylate (normal emulsifier concentration). After a rapid rise to a maximum value (period I), log v_{Br} decreases almost linearly. With increasing

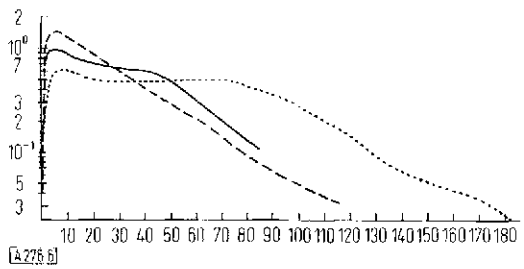


Fig. 6. Effect of the concentration of emulsifier (Na lauryl sulfate) on emulsion polymerization of methyl acrylate.
(1.3 mole of methyl acrylate/kg of emulsion; 0.5×10^{14} eV/min per g of emulsion)
– – – – 7.7 mmoles/kg of solution
——— 45.8 mmoles/kg of solution
. . . . . 90.2 mmoles/kg of solution
Ordinate: Logarithm of the overall rate of reaction [mg of polymer formed per g of emulsion every 30 sec]
Abscissa: Time [min]

emulsifier concentration, two periods (II and III) of different slope appear. With even greater increases in the concentration of emulsifier, period II becomes longer and flatter. At the highest concentrations studied, a long period of constant rate was observed.

The maximum overall rate of reaction is always reached within 5–7 minutes. Remarkably, it was greatest at the lowest emulsifier concentration, and decreased constantly as the emulsifier concentration rose. According to *Okamura* and *Motoyama* [40], an optimum emulsifier concentration exists at which the overall rate of reaction is highest. For all the monomers they investigated, *Krischan* and *Margaritova* [42] found a limiting emulsifier concentration above which the overall rate of reaction is independent of the emulsifier concentration.

The number of particles per ml of latex increases with increasing emulsifier concentration; at the same time, the particle diameter decreases. At the highest emulsifier concentrations, the particles were so small that they could no longer be counted even under the ultramicroscope. The molecular weight of the polymers increased with increasing emulsifier concentration. However, no values were determined during the early stages of the emulsion polymerization.

Figure 7 shows the influence of monomer concentration at constant emulsifier concentration on the function (log v_{Br})/t. At low monomer concentrations (41.7 g/kg of emulsion), the greater part of the monomer was dissolved in the water. Here log v_{Br} takes a simple course. After reaching the maximum, the overall rate of reaction decreases following nearly the first order with respect to the monomer concentration in the particles. With increasing initial monomer concentration, the maximum overall rate of reaction increases and is attained somewhat sooner. Figure 7 also shows that at

[40] *S. Okamura* and *T. Motoyama*, Chem. High Polymers (Tokyo) *12*, 102 (1955); Chem. Abstr. *51*, 1645 (1957).

[41] *H. Gerrens*, personal communication.

[42] *T. Krishan* and *M. Margaritova*, J. Polymer Sci. *52*, 139 (1961).

high monomer concentrations, the decrease in the overall rate of reaction after the maximum becomes slower. Again periods II and III occur, each having different slopes, and being separated by a more or less distinct break.

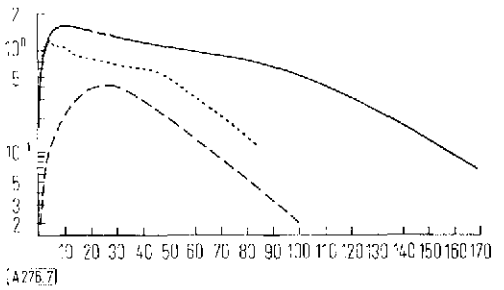


Fig. 7. Effect of the concentration of monomer on emulsion polymerization of methyl acrylate (0.5×10^{14} eV/min per g of emulsion; 40–50 mmoles of Na lauryl sulfate/kg of solution).
——— 3.0 moles of methyl acrylate/kg of emulsion
..... 1.3 moles/kg
– – – 0.485 mole/kg
Ordinate: Logarithm of the overall rate of reaction [mg of polymer formed per g of emulsion every 30 sec]
Abscissa: Time [min]

For concentrations below 1.5 mole of methyl acrylate per kg of emulsion, a plot of log $v_{Br,\,max}$ versus log [M] (Fig. 8) yields a straight line with a slope of 0.8:

$$v_{Br,\,max} \sim [M]^{0.8}$$

At higher monomer concentrations, the maximum overall rate of reaction remains constant.

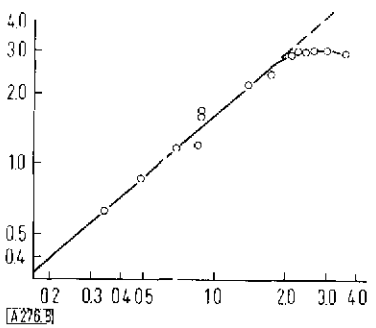


Fig. 8. Effect of the concentration of monomer on the maximum overall rate of reaction (0.5×10^{14} eV/min per g of emulsion; 45 mmoles of Na lauryl sulfate/kg of solution).
Ordinate: Maximum overall rate of reaction [mg of polymer formed per g of emulsion per min]
Abscissa: Methyl acrylate [mole/kg]

The results of these measurements still permit no definite statements to be made as to the causes of the very complex, and partly contradictory, behavior of methyl acrylate in the emulsion polymerization induced by γ-radiation. Essentially, the gel effect, polymerization in the aqueous phase, and prolonged particle formation appear to determine the kinetics. Three findings supply evidence for the appearance of the gel effect even in the early stages of the emulsion polymerization:

1. The decreasing value of the maximum overall rate of reaction with decreasing particle size (increasing emulsifier concentration). The chance of combination of radical chain ends is larger with small particles than with large ones.

2. The sharply increasing values of the maximum overall rate of reaction with increasing monomer:water ratios (increasing monomer concentration). Because the latex particles become larger, the gel effect becomes stronger.

3. The increase of the overall rate of reaction corresponding to approximately $I^{0.5}$, when the dose rate is increased at various stages of the reaction. This effect can, however, also be interpreted as being due to the polymerization in the aqueous phase, and thus to the formation of new particles.

The initiation of emulsion polymerization in the aqueous phase results from the high solubility of methyl acrylate in water (0.57 mole/l at room temperature). With average monomer:water ratios, 1 ml of emulsion contains about 10^{20} molecules of monomer and about 10^{18} micelles in the aqueous phase at the start of the polymerization. The observed rise in the overall rate of reaction with an increase in the dose rate must therefore be attributed, in the early stages of the polymerization at least, to an increased number of particles resulting from polymerization of dissolved monomer.

The free monomer phase (droplets) disappears at about 15 % conversion [calculated from the solubility of six to seven parts of methyl acrylate in one part of poly(methyl acrylate)]. From this point onwards, the monomer concentration in the polymerizing particles diminishes. However, during these early stages of the reaction, it is still high enough in the aqueous phase for further particles to be formed there. With increasing conversion, the gel effect gains significance. The course of period II is thus determined by the lowering of the monomer concentration in the latex particles, by the gel effect, and by the continuous formation of particles. High emulsifier concentrations therefore lead necessarily to a flattening and lengthening of this period (Figure 6). Although the gel effect is smaller in the smaller particles, the aqueous phase still has enough emulsifier available for particle formation to take place, even at increasing conversions. This was confirmed by a soap titration. In the same way, high monomer concentrations must necessarily result in a flattening and lengthening of period II, since the gel effect increases with growing particle size. The significance of the break between periods II and III (at 30–40 % conversion) and the role of initiation during period III are still unknown.

If the emulsifier concentration is kept constant and the monomer concentration reduced so far that the monomer is distributed almost entirely between the solution and the micelle phase, the polymerization is supplied from the very beginning both from the solution and from the monomer-filled micelles. The solution then becomes rapidly depleted of monomer, and the monomer-filled micelles also disappear, since they have given up their monomer to growing particles. Both of these effects result in a lower maximum overall rate of reaction than that encountered at higher monomer concentrations (broken curve in Figure 7).

At the same time, the particles are smaller, and hence the gel effect is lower. Finally, no more particles are formed. The overall rate of reaction thus decreases after the maxi-

mum to approximately the first order with respect to the monomer concentration in the particles.

γ) Influence of Temperature

A curve of v_{Br}/t was taken at 15, 25, and 50 °C (see Table 7). In none of these measurements could any significant effect of temperature be detected.

Table 7. Effect of temperature on emulsion polymerization of methyl acrylate induced by γ-radiation (0.5×10^{14} eV/min per g of emulsion; 1.3 mole of methyl acrylate/kg of emulsion; 45–46 mmoles of Na lauryl sulfate/kg of solution).

Temp. [°C]	$v_{Br, max}$ [mg of polymer/min/g of emulsion]	Slope of curve [*] in period II	Slope of curve [*] in period III	Molecular weight of polymer
15	2.2	0.45	1.50	1.62×10^6
25	2.2	0.51	1.54	1.62×10^6
50	1.9	0.46	1.26	1.58×10^6

[*] In arbitrary units.

δ) Rate of Radical Formation and $G_{polymer}$

If it is assumed that polymerization of methyl acrylate induced by γ-radiation also proceeds via free radicals formed almost completely in the aqueous phase and thus at a high G value of 6.7 [29], then at a dose rate of about 2×10^{14} eV/min per gram of emulsion, $\rho \approx 1.2\times10^{13}$ radicals per minute per gram of emulsion. In one such experiment, 1.85×10^{14} particles per ml were counted at the end of the polymerization. It may be assumed that the majority of the particles are already present by the time the pure monomer phase disappears. The system therefore contains about 10^{14} particles after ten minutes. During this same time, a total of 1.2×10^{14} radicals have been formed. If the assumptions on which these calculations are based are correct, then during the initial stages of emulsion polymerization, each radical induces formation of one polymer chain. The average molecular weight at the end of the reaction amounted to about 1.5×10^6. If this value is used to calculate the value of $G_{polymer}$ during the maximum overall rate of reaction (4.4 mg/min per gram of emulsion), the improbably high number of 146 polymer molecules per radical or a value for $G_{polymer}$ of 875 is found. An experimental explanation for this does not yet exist. Transfer reactions to the monomer, direct initiation of polymerization by excited molecules, or even too high a molecular weight in the equation, could all contribute to this high radical yield. Without determinations of the number of particles and of the molecular weight of the polymer at various stages of the reaction, the question of the radiation-chemical yield cannot be settled.

h) Grafting of Emulsion Polymers

Latices containing radicals which are still active can be grafted by the addition of monomer. Such radicals may have been carried over from the emulsion polymerization and may be enclosed within the particles, or may be formed subsequently in the polymer particles by ionizing radiation. If the irradiation is actually carried out in the presence of monomer [43], then large amounts of homopolymer generally result. If, on subsequent addition of monomer M, homopolymer M_n is found in the reaction product, then transfer to monomer has occurred.

Allen et al. [38] polymerized vinyl acetate at 20 °C in aqueous emulsion with sodium dioctylsulfosuccinate as emulsifier, using ^{60}Co γ-radiation until the system reached a conversion of 70 %. After about half an hour, the latex was mixed with a methyl methacrylate emulsion, and the reaction allowed to proceed at 40 °C. Both processes were followed dilatometrically. About 1 % of the methyl methacrylate was converted. The polymers were titrated turbidimetrically. It was thus found that the mixture contained considerable quantities of poly(methyl methacrylate) along with graft or block copolymers. By this method [44], appreciably more copolymer (50–100 mg/g of vinyl acetate) is formed than can be calculated from an assumed average radical concentration of 0.5 per particle of the poly(vinyl acetate) dispersion. In addition, a very large amount of poly(methyl methacrylate) was found. These results led to the conclusion that numerous transfer reactions take place in the polymerizing system when it is outside the radiation field: transfer to monomer, to poly(vinyl acetate) causing the formation of graft copolymer, and also to poly(methyl methacrylate) leading to branching [39].

The polymer mixtures were separated by column chromatography. The mixture (1 g) was added to 100 ml of glass beads of 0.1 mm diameter and eluted with acetone/water mixtures at 25 °C, the proportion of acetone being gradually increased.

The poly(vinyl acetate) latices originally contained ca. 5×10^{15} particles/l [44a]. On the assumption – not proven for this case – that the average concentration of radicals per particle = 0.5, the radical concentration can be ascertained to be 2.5×10^{15} per liter of latex. From this value, kinetic chain lengths for the polymerization with methyl methacrylate can be calculated to be 2×10^8 (for 1 ml of methyl methacrylate/11.25 ml of 12.5 % dispersion) and 3×10^9 (for 16 ml of methyl methacrylate/11.25 ml of 12.5 % dispersion), both at 25 °C. It thus appears that the kinetic chain length under the experimental conditions is governed only by the quantity of methyl methacrylate added, and that practically no mutual termination of the growing chains (in neighboring particles) takes place. The yield of poly(methyl methacrylate) at 25 °C was independent of the quantity of methyl methacrylate added and amounted to 15 % of the total polymer, but increased with temperature. The yield of graft copolymer rose with the methyl methacrylate concentration. Probably only a very small part of the copolymer isolated consisted of initially formed block copolymer. The growing chains of the block copolymer are terminated very rapidly by transfer

[43] Brit. Pat. 883473 (Nov. 29th, 1961), Société Anonyme Nobel-Bozel.

[44] *P. E. M. Allen, G. M. Burnett, J. M. Downer, J. Hardy* and *H. W. Melville*, Nature (London) *182*, 245 (1958).

[44a] This value seems very low in view of the relatively high concentration of emulsifier.

reactions to monomer or to poly(vinyl acetate). The yield of graft copolymer is determined by the competition of poly(vinyl acetate), methyl methacrylate, and later of poly(methyl methacrylate), for the radical chain ends.

If a pre-irradiated film of poly(methyl methacrylate) is dipped into a styrene emulsion, only a small amount of copolymer can be detected afterwards in the film [38]. However, vigorous polymerization occurs in the emulsion. The endothermic heat of the overall reaction is 7.2 kcal/mole; this corresponds to the activation energy of the propagation reaction in the emulsion polymerization of styrene. The molecular weight of the resulting polymer, 4×10^6 to 12×10^6, was very high. These observations are very interesting and must be interpreted as showing that block copolymerization in the poly(methyl methacrylate) film is quickly terminated by transfer to monomer. The radicals are at first quite small (oligomeric) and escape into the emulsion and grow there without disturbance to give monomer-polymer particles. Since the molecular weights measured lay far beyond the number average which is given as the upper limit by the transfer constant, it is necessary to assume that transfer reactions to monomer, then to polymer, and back again to monomer occur in a single particle, giving a highly branched polymer. If grafting with styrene is attempted on a radiation-polymerized poly(vinyl acetate) latex, the predominant product is again polystyrene [39].

Schneider et al. [45] produced radicals by irradiating a catalytically polymerized poly(methyl methacrylate) dispersion and investigated the effect of the reaction conditions on the course of a grafting reaction with acrylonitrile. Although transfer reactions to monomer apparently played a large role in the experiments of *Allen* et al., *Schneider* et al. were able to show that no polyacrylonitrile is formed in the system poly(methyl methacrylate)/acrylonitrile, so that there is practically no transfer to the acrylonitrile. (For methods of grafting pre-irradiated dispersions, see also [46]).

4. Determination of Reaction Constants in Emulsion Polymerizations Induced by γ-Radiation

Radiochemically initiated polymerizations offer the very interesting possibility of varying the frequency of initiation during the reaction almost at will. In homogeneous systems, the well-known "method of rotating sectors" is used for determining reaction constants. In this method, the beam of initiating ultraviolet radiation is interrupted by a rotating sector, so that the polymerization of the monomer is initiated in pulses, and the reaction has enough time to cease before the next flash of light renews polymerization. From the results of these measurements in the non-steady state it is possible to determine chain lengths and lifetimes of radicals, *inter alia*.

This elegant method is not applicable to emulsion polymerization under normal conditions, since ultraviolet light cannot illuminate an emulsion homogeneously. It can be used, however, with ionizing radiation, especially X-rays or γ-rays. Here, a non-steady state is obtained by changing the intensity of radiation or, in the limiting case, by introducing and withdrawing the source. However, the equations developed for the kinetics of the non-steady state in homogeneous phase (*Bamford* et al. [47], p. 20) cannot be directly applied to the non-steady state in emulsion polymerization. Such equations are based on the assumption of chain termination by radical combination; termination by initiator radicals or transfer reactions are not ordinarily considered. It is especially important that the reaction volume under consideration be very large, whereas in emulsion polymerization, the system is divided into innumerable small reaction volumes, between which, according to the earlier interpretation, no interaction, especially no radical diffusion, should occur. (An opposing view has been expressed by *Krischan* and *Margaritova* [42]). In such a small reaction volume, there can never be as many radicals near each other as in the large volume of a homogeneous system; when initiation ceases, therefore, the limiting state of "one radical or no radical" is soon reached. In this connection, a special case is provided by systems which tend to have a strong gel effect and which involve relatively large latex particles. Here the average concentration of radicals per particle can rise significantly above the theoretical value of 0.5 (for systems with very rapid chain termination).

In the case of styrene, any decrease in the concentration of initiator or in the dose rate during the period of zero order, or, in general, after the conclusion of particle formation, should cause no diminution in the overall rate of reaction. Instead, the reaction should proceed to the end without change, provided that there is neither a gel effect nor any interaction between the particles. The average concentration of radicals remains 0.5 per particle.

In systems in which the average radical concentration is greater than 0.5/particle, it will decrease to the average value of 0.5 when initiation ceases because of termination of the growing chains in the particles. As a consequence, there is a corresponding decrease in the overall rate of reaction, but even here it should not fall to zero when initiation is interrupted, as in homogeneous systems (where, at the end, "one or no radical" remains in the entire reaction volume in the limiting case).

The few experimental results available up to the present time for emulsion polymerizations induced by γ-rays are surprising and contradictory. From the work of *Allen* et al. [38,39,44], it appears that emulsion polymerization continues until the monomer is consumed, even after initiation ceases, so that no mutual termination between the latex particles takes place. It can be gathered from the curves of *Meshirova* et al. that if the radiation source is turned off at moderate conversions,

[45] *Christel Schneider, J. Herz,* and *D. Hummel,* Makromolekulare Chem. *51*, 182 (1962).

[46] Franz. Pat. 1193689 (May 4th 1959), Monsanto Chemicals Ltd.

[47] *C. H. Bamford, W. G. Barb, A. D. Jenkins,* and *P. F. Onyon:* The Kinetics of Vinyl Polymerization by Radical Mechanisms. Butterworths Sci. Publ., London 1958.

the reaction rate falls off only after a delay. According to these authors, after-polymerization can continue for up to an hour, whereby 15–20 % of the monomer are converted.

We [30] found a strong decrease in the overall rate of reaction with both styrene and methyl acrylate when the ^{60}Co source was removed after moderate conversions (remaining intensity 0.15 rad/hr). It can be seen from Figure 9 that the overall rate of reaction for methyl acrylate falls off during period II, within about 15 minutes, to less than $^1/_{10}$ of its original value when the frequency of initiation has fallen to about $^1/_{1000}$. If the source is restored, the overall rate of reaction rises once more to the value which would have been attained at the same conversion with continuous irradiation.

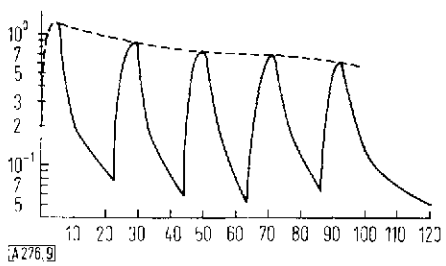


Fig. 9. Emulsion polymerization of methyl acrylate catalysed by intermittent irradiation.

($I_1 = 0.5\times10^{14}$ eV/min per g of emulsion; $I_2 = 1.5\times10^{11}$ eV/min per g of emulsion; 1.35 mole of methyl acrylate/kg of emulsion; 45 mmoles of Na lauryl sulfate/kg of solution).

Ordinate: Lugarithm of the overall rate of reaction [mg of polymer formed per g of emulsion every 30 sec]
Abscissa: Time [min]

As already stated, a strong gel effect can be assumed to set in quite early with methyl acrylate, with the result that the average concentration of radicals per particle rises considerably. Interruption of the initiation therefore leads to a non-steady state similar to that in homogeneous polymerization. This is also true for the resumption of polymerization during period II. We assumed that the formulae derived for non-steady states in homogeneous polymerization can also be applied here. We determined the pre-effect using the extrapolation method [48] (Figure 10).

From the equations for a non-steady state [47], k_p/k_t was calculated for methyl acrylate to be 0.084 (average of 15 measurements). The values obtained from the pre- and after-effects were in good agreement (Table 8).

A quite unexpected observation, which is still not fully explained, is the fact that, even with styrene, a decrease in the frequency of initiation to about $^1/_{1000}$ of its original value results in a sharp drop in the overall rate of reaction, and that similar values are obtained for

[48] *G. M. Burnett*, Trans. Faraday Soc. *46*, 772 (1950).

Table 8. Quotient k_p/k_t of the reaction constants in emulsion polymerization of styrene and methyl acrylate at 25 °C induced by γ-radiation (see also Table 3).

Calculated from	Styrene	Methyl acrylate
Pre-effect	0.089	0.085
After-effect	0.089	0.084

k_p/k_t from the pre-effect (Figure 10) and after-effect (Table 8; eight measurements). This finding, if not caused by the diffusion of inhibitors into the reaction

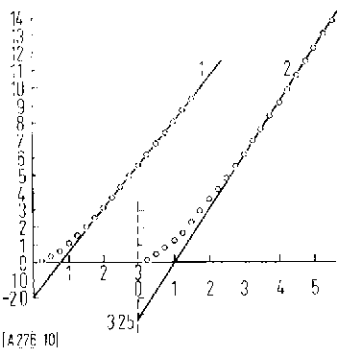


Fig. 10. Pre-effect in emulsion polymerization induced by γ-radiation.
Curve 1: Styrene
Curve 2: Methyl acrylate
Ordinate: Change in monomer concentration [mg/g of emulsion]
Abscissa: Time [min]

zone, is inconsistent with the present ideas concerning the emulsion polymerization of styrene. It must be assumed either that the radicals can leave the monomer-polymer particles as easily as they enter, or that chain termination occurs by combination of growing particles (with a reduction in the number of particles!) as postulated by *Medvedev* et al. [49] and by *Krischan* and *Margaritova* [42]. Both assumptions contradict most of the experimental findings. It is necessary to examine the effect of interrupting the initiation at various stages of emulsion polymerization of poorly water-soluble monomers on the overall rate of reaction, the number of particles, and the average molecular weight.

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[49] *S. S. Medvedev, P. M. Khomikovsky, A. P. Sheinker, E. V. Zabolotskaya*, and *G. D. Berezhnoy*, Sbornik Problemy Fiz. Khim. *1*, 1 (1958).

Syntheses with *s*-Triazine

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The preparation and properties of s-triazine are discussed. Nucleophilic reagents (even water) readily attack s-triazine. Thus, open-chain and heterocyclic compounds, e.g. formamidines, aminomethylene compounds, and triazole, pyridine, and pyrimidine derivatives are accessible from s-triazine. With amidines and imido ethers substituted triazines are obtained (by trans-triazination). The latter are formed via open-chain intermediates.

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  3. From thioformamide
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I. Introduction

Although derivatives of *s*-triazine were among the earliest known heterocyclic compounds (cyanuric acid, *Scheele* 1776), the preparation of the parent compound was achieved comparatively late. *Grundmann* and *Kreutzberger* [1] prepared *s*-triazine in 1953 by treating the well-known adduct of hydrogen chloride and hydrogen cyanide with a base. They found the compound to be identical with a substance which had already been obtained by *Nef* [2] in 1895 from formimido ethyl ether and which had erroneously been assigned the structure of a dimer of hydrogen cyanide. *Willstätter* [3] had also unwittingly obtained *s*-triazine as a product of thermolysis of thioformamide. The unusual properties of *s*-triazine, especially its instability in the presence of water, an uncommon property for a nitrogenous heterocyclic compound, explain the numerous failures of early attempts to synthetize *s*-triazine by classical methods [4]. Ultimately, this led to the conclusion that the compound could only exist in the form of complex salts with metals [5].

II. Preparation of *s*-Triazine

1. From Formimido Ethers

The oldest method for preparing *s*-triazine [1] involves elimination of alcohol and hydrogen chloride from formimido ethyl ether *(2a)* by means of solid sodium hydroxide suspended in ether [2]; *Cramer* [6] was the first to modify this procedure to make it useful for preparative purposes. He used the benzyl ether *(2b)* and diethylaniline as base. *Schaefer* [7] has shown recently that excellent yields can also be obtained from the ethyl ether *(2a)* with tertiary aliphatic bases. The use of homologous aliphatic formimido ethers is possible, but offers no advantages. Of the bases investigated, tri-n-butylamine has proved to be best.

[1] *Ch. Grundmann* and *A. Kreutzberger*, J. Amer. chem. Soc. *76*, 632, 5646 (1954).

[2] *U. Nef*, Liebigs Ann. Chem. *287*, 337 (1895).

[3] *R. Willstätter* and *T. Wirth*, Ber. dtsch. chem. Ges. *42*, 1915 (1909).

[4] For reviews of earlier work, see *W. Ruske*, Chem. Technik *5*, 308, 368 (1953); *6*, 489 (1954).

[5] *P. Pascal*, C. R. hebd. Séances Acad. Sci. *180*, 1850 (1925).

[6] *F. Cramer, K. Pawelzik*, and *J. Kupper*, Angew. Chem. *68*, 649 (1956).

[7] *F. C. Schaefer* and *G. A. Peters*, J. org. Chemistry *26*, 2778 (1961).

2. From Formamidine

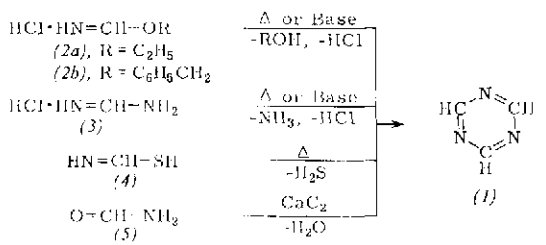
s-Triazine can also be prepared analogously by elimination of ammonia and hydrogen chloride from formamidine hydrochloride *(3)* by treatment with basic reagents [8] or by dry distillation [1]. Tertiary aliphatic amines, *e.g.*, tri-n-butylamine, seem to give better yields than aromatic bases such as quinoline or diethylaniline. In either case, the yield can be improved significantly by employing a vacuum [9].

3. From Thioformamide

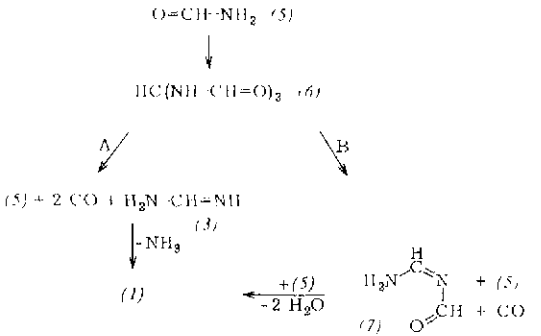
This method, first described by *Willstätter* [3], cannot be recommended, in spite of the fact that by working up the product carefully, the yield can be made to approach 60 % [10]. The preparation of large amounts of thioformamide *(4)* is difficult and time-consuming.

4. From Formamide

A direct synthesis of *s*-triazine by elimination of water from three molecules of formamide *(5)* with consequent cyclization has recently been developed. Calcium carbide in the presence of catalytic amounts of a transition metal halide, *e.g.*, ferric chloride, serves as dehydrating agent. A side reaction that cannot be prevented is the base-catalysed decomposition of *(5)* to give carbon monoxide and ammonia. The yield is therefore only 19 % [11].



An improved synthesis of *s*-triazine from formamide has been described by *Bredereck* [12]. Alkylating agents, especially dimethyl sulfate, react with formamide *(5)* to form tris(formylamino)methane *(6)*. *s*-Triazine is obtained from the latter in moderate yield by thermolysis either directly or preferably in an excess of formamide [13]. The mechanism of formation has not been completely elucidated; *(6)* either decomposes into formamide, carbon monoxide, and formamidine (Scheme 1, Reaction A), which is then converted into *s*-triazine (cf. Section II.6), or else to formamide, carbon monoxide, and *N*-formylformamidine *(7)* (Scheme 1, Reaction B), which then reacts with formamide with loss of water to give *s*-triazine.



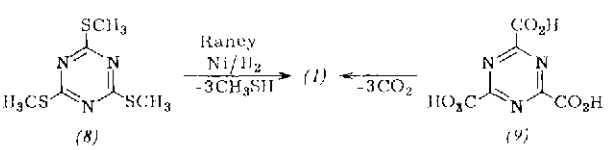
Scheme 1. The formation of *s*-triazine

Since *Bredereck* obtained higher yields of *s*-triazine than are to be expected from Scheme 1. A (compare, however, [13]), he assumed that the reaction proceeds according to B, although the sensitivity of *(1)* towards water makes its formation from *(7)* and formamide rather unlikely. From analogous reactions, it should be assumed that the equilibrium $(1) + 2H_2O \rightleftharpoons (5) + (7)$ is shifted very strongly to the right.

Although the yields are lower in the syntheses starting from formamide than in the methods described in Sections II.1 and II.2, the methods starting from formamide are still useful, because they allow the preparation of *s*-triazine from readily available starting materials without requiring the use of hydrogen cyanide [14].

5. From Compounds with a Preformed *s*-Triazine Ring

The formation of *s*-triazine by reductive desulfurization of trimethyltrithiocyanurates *(8)* [15] and by decarboxylation of *s*-triazine-2,4,6-tricarboxylic acid *(9)* [16] were important for the structural assignment of *(1)*, but have no preparative significance.



The situation is different for the preparation of *s*-triazine from the adducts of hydrogen cyanide and hydrogen chloride. According to recent investigations, a hexahydro-*s*-triazine structure must be assigned to these adducts [1, 17]. Hydrogen cyanide and hydrogen chlo-

[8] *Ch. Grundmann, H. Schroeder*, and *W. Ruske*, Chem. Ber. *87*, 1865 (1954).

[9] *F. C. Schaefer, I. Hechenbleikner, G. A. Peters*, and *W. P. Wystrach*, J. Amer. chem. Soc. *81*, 1466 (1959).

[10] *Ch. Grundmann*, unpublished results.

[11] *C. L. Sloan* and *W. A. Barber*, J. org. Chemistry *27*, 1073 (1962).

[12] *H. Bredereck, R. Gompper, H. Rempfer, H. Keck*, and *K. Klemm*, Angew. Chem. *70*, 269 (1958); *H. Bredereck, R. Gompper, H. G. v. Schuh*, and *G. Theilig*, *ibid. 71*, 753 (1959); see also: *H. Bredereck* in *W. Foerst:* Neuere Methoden der präparativen organischen Chemie. Verlag Chemie, Weinheim/Bergstr. 1960, Vol. III, p. 163; *H. Bredereck, O. Smerz*, and *R. Gompper*, Chem. Ber. *94*, 1883 (1961).

[13] We have tried several times to prepare *s*-triazine according to this method but have never obtained more than half of the reported yields. The yield may possibly be strongly dependent upon the quality of the formamide.

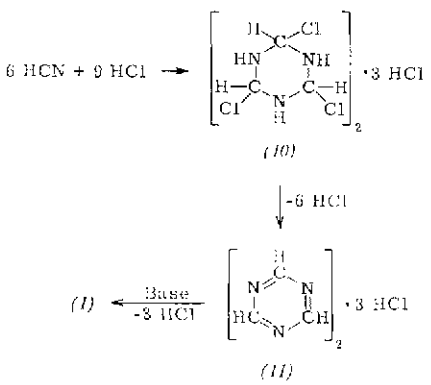
[14] Formamidine hydrochloride can also be prepared in good yield by desulfurization of thiourea with Raney nickel in the presence of ammonium chloride: *D. J. Brown*, J. appl. Chem. *2*, 202 (1952).

[15] *Ch. Grundmann* and *E. Kober*, J. org. Chemistry *21*, 641 (1956).

[16] *Ch. Grundmann* and *E. Kober*, J. org. Chemistry *21*, 1392 (1956).

[17] *Ch. Grundmann* and *A. Kreutzberger*, J. Amer. chem. Soc. *77*, 44 (1955).

ride form the "sesquihydrochloride of hydrogen cyanide" in quantitative yield. This compound is presumably a sesquihydrochloride of 2,4,6-trichlorohexahydro-*s*-triazine *(10)*. It readily loses two-thirds of its hydrogen chloride content and aromatizes to form the sesquihydrochloride of *s*-triazine *(11)*, *e.g.*, on standing over alkali in a desiccator or on subliming *in vacuo*. On heating with tertiary amines, *(10)* and *(11)* give *s*-triazine in good yield [1, 18].

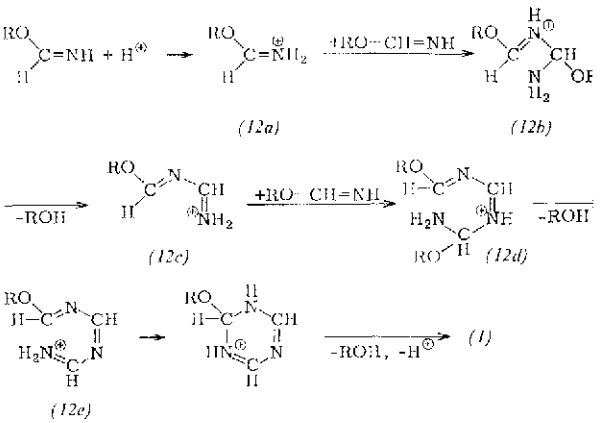


In contrast to the methods described in Sections II.1 and II.2, tri-n-butylamine offers no advantage over technical grade quinoline. The yield can, however, be increased significantly by first converting *(10)* into *(11)*. This has the advantage that only one-third of the amount of base normally required is used [10]. This method of preparation is one of the best if there is no objection to working with HCN; furthermore, any desired amount of hydrogen cyanide can be converted without danger into the non-toxic sesquihydrochloride, which can be stored conveniently.

6. Mechanism of the Formation of *s*-Triazine

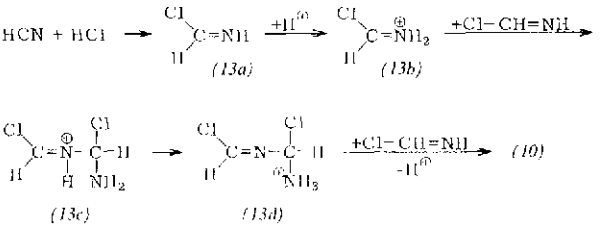
The various modes of formation of *s*-triazine described in Sections II.1–II.4 are formally very similar; a formic acid derivative of general formula HN = CHR (R = O-alkyl, NH_2, SH, OH) splits off RH, and the residue HNC trimerizes. Although it was formerly assumed that an activated, polar form of hydrogen cyanide occurred as intermediate and polymerized rapidly to form *s*-triazine, it is now believed that the reaction proceeds via stepwise condensation and a final ring closure (Scheme 2).

In the example given in Scheme 2, the first step is protonation of the imide nitrogen. The imidonium ion *(12a)* then adds onto the polarized carbon of the free imido base to form the dimer *(12b)*, which loses a molecule of alcohol and simultaneously undergoes a shift in charge. The process is repeated with the new imidonium ion *(12c)*. The driving force behind the ring closure of the open trimer *(12e)* is the gain in energy obtained by resonance stabilization of the quasi-aromatic compound *s*-triazine. The trimerization of formamidine or thioformamide can be explained in the



Scheme 2. Formation of *s*-triazine by stepwise condensation and ring closure

same way. The formation of the sesquihydrochloride of trichlorohexahydro-*s*-triazine from hydrogen cyanide and hydrogen chloride probably follows a similar course. Here the first step is the addition of HCl to form imidoformyl chloride *(13a)*, followed by protonation to give the imidonium ion *(13b)* and addition of another mole of *(13a)* to form the intermediate *(13c)*.



In contrast to the reaction mechanism discussed above, here only a prototropic shift occurs to *(13d)*; no elimination of HCl takes place. The preferential formation of the trimer rather than the linear polymer must be explained here as being due to steric influences [7, 9].

III. Properties of *s*-Triazine; Electrophilic Substitution

s-Triazine forms colorless, strongly refractive, rhombohedral crystals (m.p. 85–86 °C, corr.) [19] and boils without decomposition at 114 °C. The vapors can be heated above 600 °C before depolymerization to hydrogen cyanide occurs. The high volatility of *s*-triazine is of importance for preparative purposes. *s*-Triazine is readily soluble in organic solvents at room temperature [20]. The recommended method of purification *viz.* distillation over sodium, must be conducted with care. Prolonged boiling with the metal causes formation of triazine-sodium compounds. They can be recognized by their bluish-green color and are presumably structurally similar to the well-known pyridine-sodium compounds.

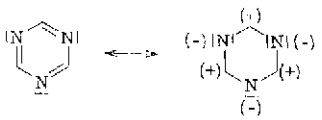
[18] *L. E. Hinkel* and *R. T. Dunn*, J. chem. Soc. (London) *1930*, 1834; *L. E. Hinkel, E. E. Ayling*, and *J. H. Beynon*, J. chem. Soc. (London) *1935*, 674.

[19] Even traces of contaminants lower the melting point significantly; the different melting points reported (between 81 and 84 °C) can thus be explained.

[20] Contrary to earlier reports [1], solutions in alcohol, and even in glacial acetic acid, are absolutely stable, at least at room temperature.

If overheating occurs near the end of the distillation, these sodium compounds may initiate an almost explosive decomposition of *s*-triazine.

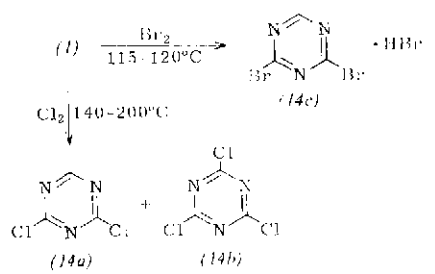
The results of physical investigations, especially infrared, Raman, and X-ray analyses, indicate an aromatic, resonance-stabilized character for *s*-triazine [21]. The ring is, however, not a regular hexagon. The only chemical indication of the aromatic character of *s*-triazine is its thermal stability. Otherwise, its properties are determined by the charge distribution. Of the two most important mesomeric forms *(1a)* and *(1b)*, the second is of greater importance.



(1a) *(1b)*

Properties that are only mildly expressed in pyridine and pyrimidine become dominant in *s*-triazine. This is especially true of its sensitivity to nucleophilic attack. Even water can be included among the nucleophilic reagents that will attack it. If a 10% solution of *s*-triazine in water is left standing at 25 °C, the compound can no longer be detected after ten minutes. The decomposition is apparently autocatalytic; *i.e.* it is base-catalyzed by the formamidine formed during hydrolysis. In the presence of dilute mineral acids, formic acid and ammonia are formed practically instantaneously.

s-Triazine shows considerable resistance to electrophilic substitution. Sulfonation and nitration are impossible, since all available reagents hydrolyse *s*-triazine at such a rate that substitution cannot occur [21a]. The temperature must attain 140–200 °C before chlorine will react to give 4% 2,4-dichloro *s*-triazine *(14a)* and 25% 2,4,6-trichloro-*s*-triazine *(14b)*. Bromine forms a stable perbromide, $C_3H_3N_3 \cdot 3Br$, at 0 °C. Substitution occurs at 115–120 °C with formation of 90% of the very reactive compound 2,4-dibromo-*s*-triazine hydrobromide *(14c)* [17].



(14a) *(14b)* *(14c)*

Since the preparation of 2,4-dihalogeno-*s*-triazines by other methods is very cumbersome and gives poor yields, bromination of *(1)* to form *(14c)* may achieve preparative interest.

[21] *J. Goubeau, E. L. Jahn, A. Kreutzberger,* and *Ch. Grundmann*, J. physic. Chem. *58*, 1078 (1954); *J. Lancaster* and *N. Colthup*, J. chem. physics *22*, 1149 (1954); *L. Siegel* and *E. Williams*, J. chem. Physics *22*, 1147 (1954).

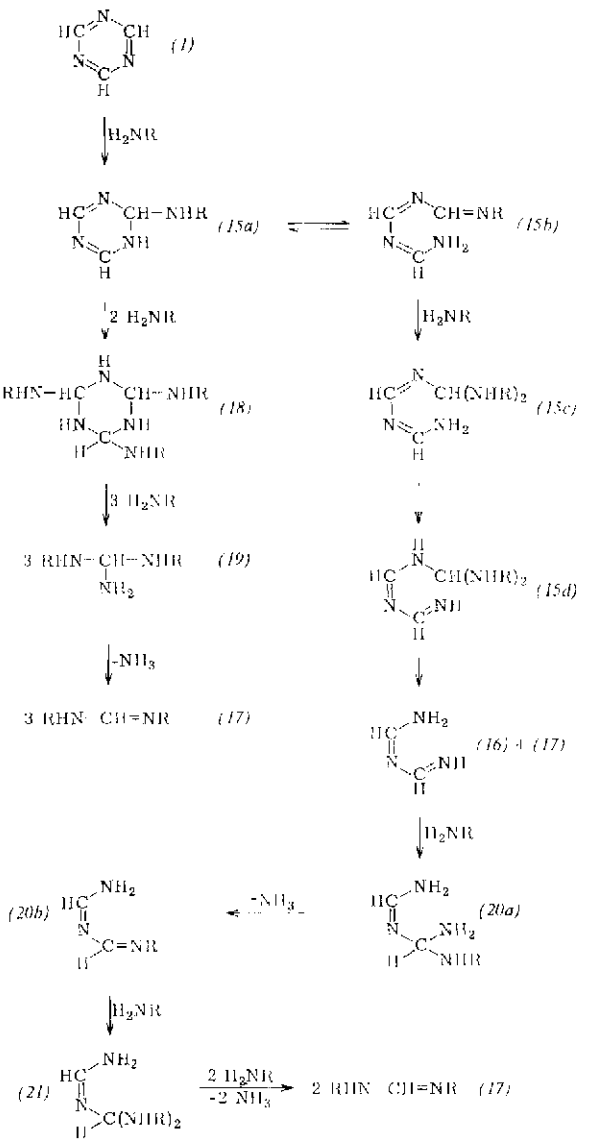
[21a] For unsuccessful attempts to prepare nitro-*s*-triazines by other methods, see *Ch. Grundmann* and *H. Schroeder*, Chem. Ber. *87*, 747 (1954).

IV. Syntheses by Nucleophilic Cleavage of the *s*-Triazine Ring (Methinylation)

True nucleophilic substitution reactions similar to those that are known and which are of preparative usefulness in the pyridine and pyrimidine series, *e.g.* the amine synthesis according to *Chichibabin*, have not yet been observed with *s*-triazine; the primary product always decomposes with cleavage of the *s*-triazine ring.

1. Cleavage with Bases

The reactions with ammonia, hydroxylamine, hydrazine, and their organic derivatives all take a similar course (Scheme 3).

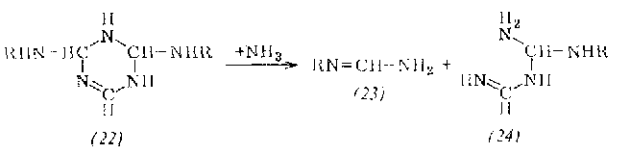


Scheme 3. Reactions of *s*-triazine with primary amines

The first step is a nucleophilic attack by the amine at the electron-deficient carbon atom. The intermediate *(15a)* has never been isolated; on the basis of the reaction between *(1)* and amidines (Section VI.6), it must be assumed that it is in equilibrium with an open-chain

isomer *(15b)*. Compound *(15b)* adds on a second mole of amine to form *(15c)*, which undergoes prototropic shift resulting in *(15d)*. One mole of a symmetrically disubstituted formamidine *(17)* is then eliminated from *(15d)* and can finally be isolated as the stable end-product. The residue, *N*-iminoformylformamidine *(16)*, immediately combines with an additional mole of amine to form *(20a)*. The reaction *(20a)* → *(20b)* is analogous to the tautomeric ring-opening reaction *(15a)* → *(15b)* and results in loss of ammonia; *(20b)* then reacts with a second mole of amine to form *(21)*. The overall result is complete cleavage of *(1)* with formation of three moles of ammonia and three moles of disubstituted formamidine.

Originally, this nucleophilic attack was formulated with the *s*-triazine ring temporarily still intact *(15a)* → *(18)*. Three additional moles of amine were then thought to cleave the ring with formation of the triaminomethane derivative *(19)*; *(19)* should then lose ammonia and the formamidine derivative *(17)* would result [22]. Although this reaction scheme cannot readily explain trans-triazinylation reactions (see Section VI.7b), it allows a better understanding of the formation of monosubstituted formamidines *(23)* or analogous compounds such as aminomethylene derivatives occasionally observed (see Section IV.7b). The intermediate *(18)* or the analogous tetrahydrotriazine compound *(22)* can decompose with formation of *(23)* and one mole of *(24)*, which then proceeds to react further.



(22) *(23)* *(24)*

2. Reaction with Ammonia

s-Triazine reacts with ammonia, anhydrous or dissolved in ethanol, only above room temperature; at temperatures higher than 100 °C complete resinification occurs. Apparently, formamidine is formed first, and, since the free base is unstable, it decomposes [23]. In the presence of an anion that can stabilize the formamidine as a salt, however, excellent yields can be obtained. Thus, *s*-triazine and ammonium chloride in boiling alcohol, for example, form formamidine hydrochloride *(25)* in quantitative yield [24].

$$C_3H_3N_3 + 3\ NH_4Cl \rightarrow 3\ H_2N{-}CH{=}NH{\cdot}HCl \qquad (25)$$

This method, however, has hardly any preparative value, since *(25)* can be obtained directly and more conveniently from the precursors of the triazine synthesis (see Sections II.1, II.2, and II.4).

s-Triazine also reacts with sodium amide with ring-opening [25]. Under fairly drastic conditions (autoclave, 160 °C in xylene), sodium cyanide and disodium cyanamide *(26)* are obtained. The presence of *(26)* has been demonstrated by converting it into di-n-butylcyanamide *(27)*.

$$C_3H_3N_3 + 3\ NaNH_2 \rightarrow 3\ NaCN + 3\ NH_3$$
$$3\ NaCN + 3\ NaNH_2 \rightarrow 3\ Na_2N{-}CN + 3\ H_2$$
(26)
$$(n\text{-}C_4H_9)_2N{\cdot}CN \qquad (27)$$

It cannot be excluded, however, that, under milder conditions, the Chichibabin synthesis of amines could also be applied to *s*-triazine. But the method would not be of preparative importance, since the three aminotriazines are more easily accessible by other routes.

3. Reaction with Amines

Tertiary amines do not react with *s*-triazine. Secondary amines should form adducts according to Scheme 3, by analogy to the reaction *(1)* → *(15a)*. However, so far such products have not yet been isolated, presumably because they decompose easily and revert to *(1)* and the starting amine. There is no possibility for the subsequent reaction *(15a)* → *(15d)*, since there is no hydrogen atom available on the amine nitrogen. Secondary amines, however, may enter as second reactant in the step *(15b)* → *(15c)*; examples of this type of reaction are described in Sections IV.3 and IV.5. Primary amines lead to ring cleavage according to Scheme 3.

a) *Primary Monofunctional Amines; Synthesis of N,N'-Disubstituted Formamidines*

Aliphatic and aromatic amines generally react very smoothly with *s*-triazine to form *N,N'*-disubstituted formamidines *(17)*. When a vigorous reaction takes place, dilution with an inert organic solvent is advisable. Normally, the reaction starts on gentle warming with evolution of ammonia and is completed when no further NH_3 is evolved. Table 1 lists disubstituted formamidines which have been prepared in this manner [23].

Table 1. *N,N'*-Disubstituted formamidines prepared from *s*-triazine and primary amines

$$C_3H_3N_3 + 6\ RNH_2 \rightarrow 3\ NH_3 + 3\ R{-}NH{-}CH{=}N{-}R \qquad (17)$$

Amine R	B.p. [°C/mm] or m.p. [°C]	Yield of Formamidine [%]
n-C_4H_9-	103–104/4 [a]	97
n-C_7H_{15}-	213–214/4 [b]	94
n-$C_{12}H_{25}$-	72–74	100
C_6H_5-	143	93
$C_6H_5CH_2$-	79	84
Cyclohexyl	106	84
p-H_2N-C_6H_4- [26]	383–386	78

[a] $n_D^{25} = 1.4632$; [b] $n_D^{25} = 1.4729$.

b) *Primary Bifunctional Amines*

α) Synthesis of Heterocycles

If the second amino group entering into the reaction *(15b)* → *(15c)* [see Scheme 3] is connected to the first by a carbon bridge in such a way that ring closure is

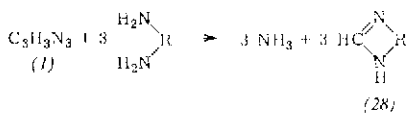
[22] *Ch. Grundmann* and *A. Kreutzberger*, J. Amer. chem. Soc. *77*, 6559 (1955); J. Polymer Sci. *38*, 425 (1959).

[23] *Ch. Grundmann* and *A. Kreutzberger*, J. Amer. chem. Soc. *77*, 6559 (1955).

[24] *Ch. Grundmann* and *R. Rätz*, J. org. Chemistry *21*, 1037 (1956).

[25] *Ch. Grundmann* and *A. Kreutzberger*, J. Amer. chem. Soc. *77*, 44 (1955).

possible, then instead of *(17)*, heterocyclic rings with nitrogen in 1,3-position *(28)* are obtained.



(28)

The reaction proceeds under the conditions described in Section IV.3a. To prevent partial loss of triazine by sublimation during reactions with slowly reacting amines, it is recommended to immerse the flask containing the reaction mixture rapidly in a heating bath at 160–180 °C so that the reaction will proceed in the shortest time possible. Heterocyclic compounds prepared in this way are listed in Table 2.

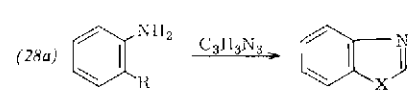
Table 2. Heterocycles of type *(28)* prepared from *s*-triazine and diamines [23]

	Diamine	Product	B.p. [°C/mm] or m.p. [°C]	Yield [%]
1	$H_2N-(CH_2)_2-NH_2$	Δ^2-Imidazoline	68–70/3 52–55 Picrate: 201–202	47
2	$H_2N-(CH_2)_3-NH_2$	3,4,5,6-Tetra-hydropyrimidine	71–73/3 Picrate: 279–280	51
3	$H_2N-(CH_2)_4-NH_2$	1,3-Diazacyclo-hept-1-ene [26]	117–118	10
4	*o*-Phenylenediamine	Benzimidazole	175	100
5	1,8-Diamino-naphthalene	Perimidine	224	100
6	4,5-Diaminopyrimidine	Purine	215–217	23
7	4,5-Diaminouracil	Xanthine	360 (dec.)	29
8	1,3-Dimethyl-4,5-diaminouracil	Theophylline	268	99
9	$H_2N-(CH_2)_2-NH-NH_2$	1,2,5,6-Tetra-hydro-1,2,4-triazine [27]	146–147/15 Picrate: 132–133	30

With the exception of examples 1, 2, 3, and 9, these compounds can also be prepared from formic acid derivatives, *e.g.*, formates, orthoformates, or formamide. In most cases the triazine method is superior to the older procedures, because the product is formed in higher yield and in greater purity. The only by-product formed is ammonia, which can easily be removed.

In this ring closure reaction, the second primary amino group can be replaced by another nucleophilic group, *e.g.*, a secondary amino, a hydroxy, or a sulfhydryl group. Several examples are given in Table 3.

Table 3. Heterocycles prepared from *s*-triazine and amines of type *(28a)*



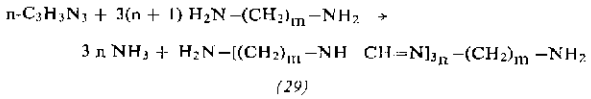
R in *(28a)*	X	Product b.p. [°C/mm] or m.p. [°C]	Yield [%]
$NHCH_3$	$N-CH_3$	60–61	50
OH	O	45/4	89
SH	S	74.5/3	85

[26] *Ch. Grundmann* and *A. Kreutzberger*, J. Polymer Sci. *38*, 425 (1959).

[27] *Ch. Grundmann* and *R. Rätz*, Chem. Ber. *91*, 1766 (1958).

β) Synthesis of Polymeric Alkyleneformamidines

s-Triazine reacts with primary diamines in which the amino groups are sufficiently distant from each other to make intramolecular ring closure unlikely, to form poly(alkyleneformamidines) *(29)* [26].

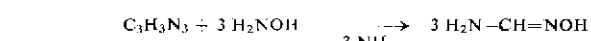


(29)

With m = 4, 5, or 6, crystalline oligomers with n = 2–5 are obtained at 80 °C. On heating to 200 °C, condensation continues by elimination of diamine to form solid polymers with n = 40–60. These poly(alkyleneformamidines) melt at 205–215 °C (m = 5) or at 250–260 °C (m = 6) and can be spun into elastic fibers, which are, however, not very stable towards acid or alkaline hydrolysis. With 1,4-butylenediamine (m = 4) about 10 % of the corresponding heterocyclic ring, 1,3-diazacycloheptene (Table 2, No. 3), is formed in addition to the polymer. With m = 5 or 6, there is so little tendency for eight- and nine-membered heterocyclic rings to be formed that the isolation of these compounds has not been possible. With *p*-phenylenediamine, the reaction stops at the *N,N'*-disubstituted formamidine, yielding *N,N'*-bis-(p-aminophenyl)formamidine (Table 1, bottom line). This is apparently due to the insolubility of this compound in the reaction mixture. On boiling in glacial acetic acid, the compound is converted into *N,N'*-diacetyl-*p*-phenylenediamine.

4. Reaction with Hydroxylamine

Free hydroxylamine and *s*-triazine react very violently; formamide oxime *(30)* can be isolated in 13 % yield from the predominantly resinous reaction mixture. Use of a diluent, *e.g.*, absolute alcohol, gives somewhat better results [10].



(30)

In contrast to free formamidine, *(30)* is so stable that it can be isolated without a stabilizing anion. This reaction is an example of the possibility discussed in Section VI.1 of cleaving the triazine ring with only one mole of a nucleophilic reagent and obtaining a monosubstituted formamidine. As is well known, the disubstituted product, *N*-hydroxyformamide oxime, HON–CH=NOH, is unstable [28]; this explains the relatively low yield of *(30)* obtained even when all precautions are strictly observed.

5. Reactions with Hydrazine and Hydrazine Derivatives

The reaction of *s*-triazine with hydrazine is much less smooth than its reaction with ammonia (cf. Section IV.2), apparently because the primary products to be

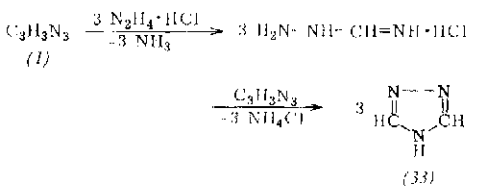
[28] *H. Wieland* and *H. Hess*, Ber. dtsch. chem. Ges. *42*, 4178 (1909).

expected, *viz.* formamide hydrazone *(31)* and formylhydrazine hydrazone *(32)*, are considerably more unstable and more reactive than formamidine [29].

$H_2N-CH=N-NH_2$ *(31)* $H_2N-NH-CH=N-NH_2$ *(32)*

a) *Synthesis of 1 2,4-Triazoles*

This instability is especially notable in the reaction of *s*-triazine with hydrazine monohydrochloride. Although the reaction with ammonia gives a quantitative yield of formamidine hydrochloride (cf. Section IV.2), here neither *(31)* nor *(32)* can be isolated as their hydrochlorides. If three moles of $N_2H_4 \cdot HCl$ to two moles of $C_3H_3N_3$ are used, apparently the hydrochloride of *(31)* is initially formed and then reacts immediately with one mole of *s*-triazine to form 1,2,4-triazole *(33)* in almost quantitative yield [24]. The second stage of the



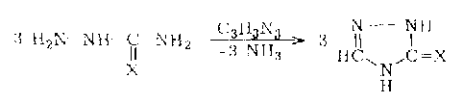
(1) *(33)*

reaction is analogous to the formation of 1,3-diazoles or 1,3-diazines from diamines (cf. Section IV.3bα). Similar to the reaction with primary-secondary diamines (cf. first example in Table 3), here the hydrochlorides of monosubstituted hydrazines can be used in place of hydrazine (examples: Table 4, Nos. 2 and 3).

Table 4. 1,2,4-Triazoles prepared from *s*-triazine and hydrazine derivatives

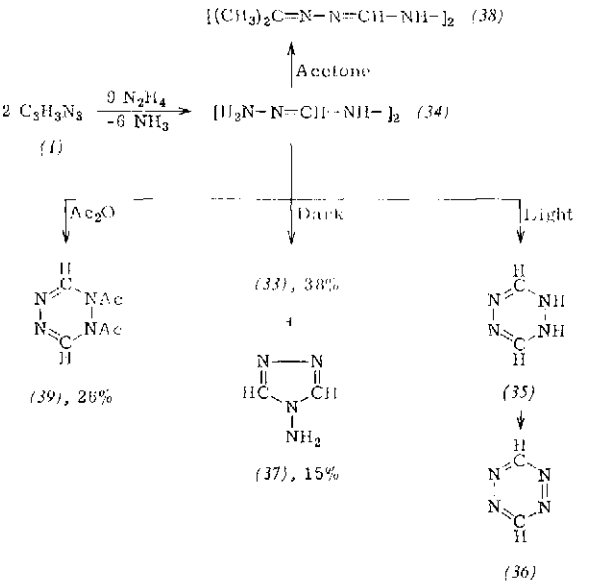
	Hydrazine	Product	M.p. [°C] or b.p. [°C/mm]	Yield [%]
1	$N_2H_4 \cdot HCl$	1,2,4-triazole	121	95
2	$H_3C-NH-NH_2 \cdot HCl$	1-methyl-1,2,4-triazole	20 175–176/760	81
3	$H_5C_6-NH-NH_2 \cdot HCl$	1-phenyl-1,2,4-triazole	47 268–270/760	83
4	$p\text{-}NO_2-C_6H_4-NH-NH_2 \cdot HCl$	1-(*p*-nitrophenyl)-1,2,4-triazole [10]	192–193	79
5	$p\text{-}Br-C_6H_4-NH-NH_2 \cdot HCl$	1-(*p*-bromophenyl)-1,2,4-triazole [10]	146	62
6	$H_2N-C(NH)-NH-NH_2$	3-amino-1,2,4-triazole	158–159	47
7	$H_2N-CO-NH-NH_2$	3-hydroxy-1,2,4-triazole	234–235	19
8	$H_2N-CS-NH-NH_2$	3-mercapto-1,2,4-triazole	215–216	63

Derivatives of 1,2,4-triazole are obtained in analogous ring closure reactions by using substituted hydrazines of type *(33a)* [30].



(33a), X = NH, O, S

The reaction of *s*-triazine with free hydrazine proceeds so violently and is so complex that it is only of limited preparative value. With ether as diluent, at room temperature, and with exclusion of air, light, and moisture, the primary product is 1,2-diformylhydrazine dihydrazone *(34)* [30] and is obtained in 80 % yield. This is a very unstable compound that was previously obtained in minute yield from hydrogen cyanide and hydrazine [31].



When exposed to light, it decomposes by cyclization to 1,2-dihydro-1,2,4,5-tetrazine *(35)*, which is then oxidized by air to form 1,2,4,5-tetrazine *(36)*. This conversion, however, is not suitable for the preparation of *(36)*, because simultaneously spontaneous decomposition (not catalysed by light) takes place. Starting from compound *(34)*, 38 % 1,2,4-triazole *(33)* and 15 % 4-amino-1,2,4-triazole *(37)* are formed. The formation of *(37)* may be explained by intramolecular ring-closure of *(34)* with elimination of hydrazine; on the other hand, *(33)* is formed only in the presence of ammonia, which, being a product of decomposition of *(34)* in the dark, is always available in abundance.

[29] In this connection, cf. *R. Rätz* and *H. Schröder*, J. org. Chemistry *23*, 1931 (1958).

[30] *Ch. Grundmann* and *A. Kreutzberger*, J. Amer. chem. Soc. *79*, 2839 (1957).

[31] *E. Müller* and *L. Herrdegen*, J. prakt. Chem. (2) *102*, 113 (1921).

Under anhydrous conditions, *(34)* may be stabilized as its dihydrochloride or by condensation with acetone to form the bis-*N*-isopropylidene compound *(38)*. Compound *(34)* can be converted into a 1,2,4,5-tetrazine derivative more smoothly by acetylation than by irradiation. With acetic anhydride, 1,2-diacetyl-1,2-dihydro-1 2,4,5-tetrazine *(39)* is obtained.

b) *Synthesis of Formazans*

While the reactions of *s*-triazine with free hydrazine are not satisfactory for preparative purposes owing to the extraordinary reactivity of the primary product *(34)*, the reactions of organic hydrazine derivatives with *s*-triazine proceed much more smoothly. As might be expected, symmetrically disubstituted hydrazines R–NH–NH–R (R = alkyl or aryl) do not react. *N,N*-Dialkylhydrazines react like primary amines, tetralkylated formhydrazidine hydrazones being formed, *e.g.*, *N,N*-dimethylhydrazine *(40)* yields 1-formyl-2,2-dimethylhydrazine 2',2'-dimethylhydrazone *(41)*, one of the few stable compounds so far known for this group.

$$C_3H_3N_3 + 6\,H_2N{-}N(CH_3)_2 \xrightarrow[-3\,NH_3]{} 3\,(H_3C)_2N{-}NH{-}CH{=}N{-}N(CH_3)_2$$

(40) *(41)*

The behavior of *N,N*-diarylhydrazines has not yet been studied; with an *N*-alkyl-*N*-arylhydrazine, *viz.* *N*-methyl-*N*-phenylhydrazine *(42)*, the reaction stops halfway. Even with an excess of *(42)* at 190 °C, the reaction does not proceed beyond N^3-methylphenylformamidrazone *(43)*.

$$C_3H_3N_3 + 3\,H_2N{-}N(CH_3){-}C_6H_5 \rightarrow 3\,H_2N{-}CH{=}N{-}N(CH_3){-}C_6H_5$$

(42) *(43)*

Monoarylhydrazines initially react in the normal way to form N^1,N^4-diarylformhydrazidine hydrazones *(44)* as expected; however, these cannot be isolated. They are oxidized by atmospheric oxygen or an excess of hydrazine to the deeply colored compound containing two hydrogen atoms less, *viz.* N^1,N^4-diarylformazan *(45)* [30].

$$C_3H_3N_3 + 6\,Ar{-}NH{-}NH_2 \xrightarrow[-3\,NH_3]{} 3\,Ar{-}NH{-}NH{-}CH{=}N{-}NH{-}Ar$$

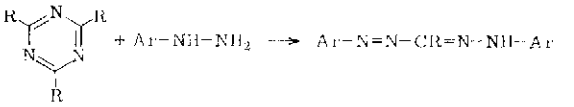
(44)

$$\xrightarrow[-H_2]{} Ar{-}N{=}N{-}CH{=}N{-}NH{-}Ar$$

(45)

In contrast to all the nucleophilic cleavages discussed in Section IV, which as far as we know, are restricted to *s*-triazine, the reaction with monoarylhydrazines can also be carried out with symmetrically trialkyl- and triaryl-substituted triazines. Some of the formazyl compounds that have been prepared in this way are presented in Table 5.

Table 5. Formazyl compounds prepared from *s*-triazines and arylhydrazines

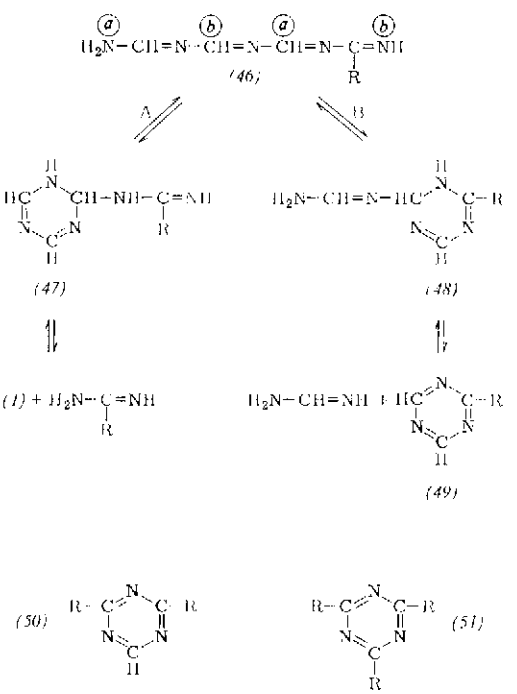


	s-Triazine R	Hydrazine Ar	Product m.p. [°C]	Yield [%]
1	H	C_6H_5	119–120	4
2	H	*p*-Br–C_6H_4	114–115	88
3	H	*p*-O_2N–C_6H_4	104–105	67
4	CH_3	C_6H_5	122–123	51
5	C_6H_5	C_6H_5	174–175	48 [a]

[a] Calculated on the basis of reacted triphenyl-*s*-triazine.

6. Reaction with Amidines and Imido Ethers; Synthesis of Mono- and Disubstituted Triazines

The reaction of *s*-triazine with amidines is of preparative importance [32]. The open-chain intermediate *(46)* formed by the addition of one mole of amidine onto one mole of triazine [analogue of *(15b)* in Scheme 3] can follow two possible routes for effecting stabilization



by ring closure. Reaction pathway A (ring closure between the atoms designated by *a*) leads to the intermediate *(47)*, which decomposes to give *s*-triazine *(1)* and the starting amidine. Pathway B (ring closure between the atoms designated by *b*) leads via *(48)* to a monosubstituted triazine *(49)* and formamidine; *(49)* is capable of reacting with an additional mole of amidine to form a compound which again has two possible modes of ring closure A and B; B leads to a disubstituted triazine *(50)*. Finally, *(50)*, too, can pass through the entire cycle to yield a trisubstitued triazine *(51)*. All these steps are probably more or less equilibrium

[32] *F. C. Schaefer* and *G. A. Peters*, J. Amer. chem. Soc. *81*, 1470 (1960).

reactions; the composition of the end-products should depend upon the reaction conditions as well as upon the gain in energy during the transitions from *(1)* to *(49)* to *(50)* and to *(51)* resulting from stabilization of the triazine ring by the groups R.

Reaction of *(1)* with imido ethers proceeds analogously [33]. The open-chain intermediate *(52)* cyclizes in accordance with B with loss of one mole of hydrogen cyanide and formation of *(53)*; alcohol is then eliminated and the monosubstituted triazine *(49)* is formed.

$$HN{=}CH{-}N{=}CH{-}N{-}CH{-}N{=}CR{-}OR' \xrightarrow[-HCN]{} \underset{(52)}{\quad}$$

$$HN{=}CH{-}N{=}CH{-}N{=}CR{-}OR' \xrightarrow[-ROH]{} \underset{(53)}{\quad} \quad (49)$$

Both procedures result in replacement of one or more methine groups in *s*-triazine by substituted methine groups. The original methine groups are eliminated as formamidine or formimido ethers (or HCN and alcohol). This reaction may therefore be called a transtriazination.

The reactions are usually carried out with the amidine hydrochlorides in the presence of alcohol. If the free bases are stable, they can also be used directly or the free amidines can be produced *in situ* from the hydrochlorides by sodium alkoxide. Occasionally fusion type reactions are employed. When imido ethers as free bases are used, addition of a weak organic acid as catalyst is advisable. From the results obtained, it appears that imido ethers yield more uniformly monosubstituted triazines than amidines do.

The simplest alkyl-*s*-triazines are most frequently obtained as mixtures of the difficultly separable substitution products *(49)*, *(50)*, and *(51)*. This does not reduce the preparative value of the procedure to any great extent, however, since mono- and disubstituted alkyl- and aryltriazines are otherwise accessible only by laborious procedures and in low yield [34]. In certain circumstances, other recent methods, such as cotrimerization of amidines or imido ethers with formamidines or formimido ethers, may be preferred [35]. These procedures are also more suitable for the preparation of symmetrically trisubstituted triazines *(51)*.

A review of the mono- and disubstituted *s*-triazines synthetized so far is given in Tables 6, 7, and 8.

Table 6. Monosubstituted *s*-triazines *(49)* prepared from amidines and *s*-triazine *(1)*

Amidine $RC(=NH)NH_2 \cdot HX$ R	X	Amidine: *(1)*	Solvent	Reaction temperature [°C]	Reaction time	Triazine Yield [%]	Triazine B.p. [°C/mm]	Triazine M.p. [°C]
$-CH_3$	Cl	5:4	acetonitrile	82	4 hr	40 [b,c]	120–130/760	[a]
$-CH_3$	free base	3:2	methanol	25	40 min	80 [b,d]	120–135/760	[a]
$-CCl_3$	Cl	1:1	acetonitrile	82	30 min	65	109/19 [e]	
$-C_6H_5$	Cl	1:1	methanol	25	18 hr	87		63–65
$-C_6H_5$	free base	3:2	methanol	25	24 hr	94		64–65
$-C_6H_5$	free base	3:1	- -	150	[g]	92 [f]		64–65
m-$O_2N-C_6H_4-$	Cl	1:1	methanol	25	18 hr	77		120–122
$C_6H_5-CH_2-$	Cl	1:1	acetonitrile	82	2 hr	34 [h]	100–105/2	
$HCl \cdot H_2N-C(=NH)-C_6H_4-(p)-$	Cl	1:2	methanol	65	2 hr	70 [i]	289–299	
CH_3O-	Cl	1:1	ethanol	78	3 hr	78	71–73/21 [k]	11
H_3CS-	I	1:1	acetonitrile	25	20 min	90	91/19	32.5
H_2N-	Cl	3:2	ethanol	78	[g]	50		224–227
C_6H_5-NH-	$CO_3/2$	3:2	ethanol	78	90 min	74		171–173
n-$C_{12}H_{25}-NH-$	OAc	1:1	ethanol	78	2 hr	46		83–84

[a] Pure methyl-*s*-triazine melts at 50–50.5 °C: *C. Grundmann* and *E. Kober*, J. org. Chemistry *21*, 641 (1956).
[b] Yield determined by mass spectroscopy.
[c] Plus 10 % dimethyl-*s*-triazine and traces of trimethyl-*s*-triazine.
[d] Plus small amounts of *s*-triazine and dimethyl-*s*-triazine.
[e] $n_D^{25} = 1.5392$.
[f] Plus 3 % diphenyl-*s*-triazine.
[g] Not reported.
[h] Plus 35 % dibenzyl-*s*-triazine.
[i] 2,2'-*p*-Phenylene-*s*-triazine.
[k] $n_D^{22.5} = 1.4936$.

Table 7. Disubstituted *s*-triazines *(50)* prepared from amidines and *s*-triazine *(1)*

Amidine $R-C(=NH)NH_2 \cdot HX$ R	X	Amidine: *(1)*	Solvent	Reaction temperature [°C]	Reaction time [hr]	Triazine Yield [%]	Triazine M.p. [°C]
$-CH_3$	free base	6:1	methanol	25	18	84 [a]	36 [e]
$-C_6H_5$	free base	1:1	acetonitrile	82	[b]	10 [c]	87–88
$C_6H_5CH_2-$	Cl	1:1	acetonitrile	82	120	35 [d]	80–82

[a] Yield determined by mass spectroscopy; plus 8 % methyl-*s*-triazine.
[b] Not reported.
[c] Plus 20 % phenyl-*s*-triazine; m. p. 61–62 °C.
[d] Plus 34 % benzyl-*s*-triazine.
[e] Pure dimethyl-*s*-triazine melts at 46 °C: *H. Schroeder* and *C. Grundmann*, J. Amer. chem. Soc. *78*, 2447 (1956).

[33] *F. C. Schaefer* and *G. A. Peters*, J. org. Chemistry *26*, 2784 (1961).

[34] *Ch. Grundmann*, *H. Ulrich*, and *A. Kreutzberger*, Chem. Ber. *86*, 181 (1953); *H. Schroeder* and *Ch. Grundmann*, J. Amer. chem. Soc. *78*, 2447 (1956); *Ch. Grundmann* and *E. Kober*, J. org. Chemistry *21*, 641 (1956).

[35] *F. C. Schaefer*, *I. Hechenbleikner*, *G. A. Peters*, and *V. P. Wystrach*, J. Amer. chem. Soc. *81*, 1466 (1959); *F. C. Schaefer* and *G. A. Peters*, J. org. Chemistry *26*, 2778 (1961).

Table 8. Mono- and disubstituted *s*-triazines prepared from imido ethers and *s*-triazine *(1)*

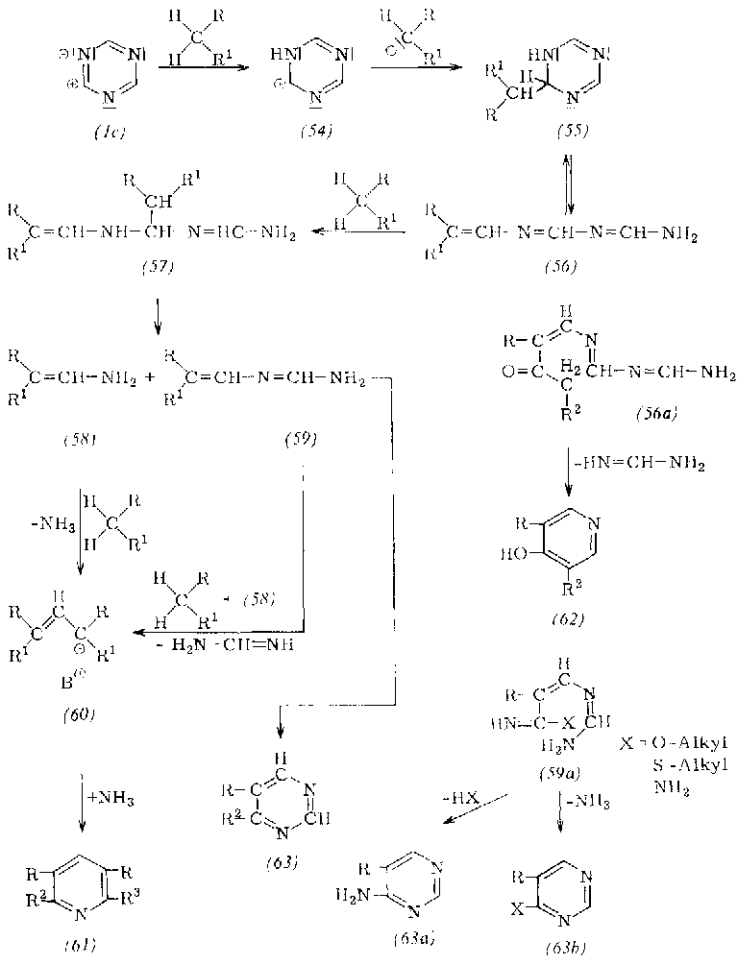
Imido ether R—C(=NH)—OR′ R	R′	Imido ether: *(1)*	Solvent and/or catalyst per mole of *(1)*	Reaction temperature [°C]	Reaction time [hr]	Yield of monosubst. triazine *(49)* [%]	Yield of disubst. triazine *(50)* [%]	B.p. [°C/mm]	M.p. [°C]
CH_3	C_2H_5	3:2	—	45	172	75 [a]	—		
CH_3	C_2H_5	3.2:2	ethanol	80	8	66 [b,c]	18 [b]		
CH_3	C_2H_5	3:1	ethanol + 1.5% H_2O	25	260	90 [a]	—		
CH_3	C_2H_5	2:1	ethanol + 0.25 mole of AcOH	50	2.5	50 [b,d]	16 [b]		
CH_3	C_2H_5	3:1	3 moles of HCl [e]	45–75	4	50 [b]	8 [b]		
C_2H_5	C_2H_5	3:2	ethanol	80	4.5	50	7	*(49)* 50–65/35 *(50)* 65–80/35	
C_6H_5	CH_3	2:1	ethanol + 0.03 mole of AcOH	80–110	32	94		105/2	62–64
m-O_2N—C_6H_4	CH_3	1:1	ethanol + 0.21 mole of AcOH	78	3	82	—		127–129
p-O_2N—C_6H_4	C_2H_5	1:1.1	ethanol + 0.2 mole of AcOH	78	3	42	—		167–169
$C_6H_5CH_2$	C_2H_5	3:2	ethanol + 1.25 moles of AcOH	80	0.75	38	7	*(49)* 135–145/25	*(50)* 71–73

[a] Determined by infrared spectroscopy.
[b] Mixture analyzed by mass spectroscopy; not separated.
[c] 26% *(1)* recovered.
[d] 35% *(1)* recovered; plus 48% trimethyl-*s*-triazine (based on imido ether).
[e] Imido ether hydrochloride.

7. Reactions with Active Methylene Groups

a) *Mechanism and Reaction Schemes*

s-Triazine must be considered as a resonance hybrid with mesomeric forms *(1a)* and *(1b)*. A polarized form *(1c)* is favored by an approaching organic compound that can donate a proton. The electron-rich nitrogen atom attracts the proton, with simultaneous formation of the carbanion of the methylene compound, which can then add onto the electron-deficient carbon atom of *(54)* to form *(55)*. Compound *(55)* is in equilibrium with the open-chain structure *(56)*. When the active methylene group is next to a $CO-CH_2$ group as in *(56a)*, elimination of formamidine and ring closure to give 4-hydroxy pyridine derivatives *(62)* can occur. In most cases, however, an additional mole of the active methylene compound adds onto *(56)*; the disubstituted intermediate *(57)* formed then decomposes to give one mole of the aminomethylene compound *(58)* and one mole of the formamidinomethylene compound *(59)*. Although an intermediate corresponding to *(59)* has so far been isolated in only one instance (R = R′ = CN), it must be assumed to exist in all cases, if the yields in subsequent reactions are to be explained. Usually only the first reaction product, the aminomethylene compound *(58)*, can be isolated.



Scheme 4. Reactions of *s*-triazine with active methylene groups

Subsequent reaction of *(58)* with an additional mole of methylene compound leads to substituted propylenes *(60)* with loss of ammonia. Since in all of these cases R = CN, these propylenes are glutaconic acid derivatives. The reaction *(58)* → *(60)* requires the presence of strong bases, hence, salts are always obtained. Subsequent reaction of the formamidinomethylene compound *(59)* with one mole of the methylene compound leads to the same products, the formamidine base released during the reaction acting as catalyst. In this reaction, formamidinium glutaconates *(60)*, where B = $CH(NH_2)_2^{\oplus}$, are formed [36]. The reaction often proceeds beyond *(60)*, because ammonia, for example, which is formed in the reaction *(58)* → *(60)*, may close the ring of the glutaconic acid derivatives *(60)* by a well-known cyclization reaction to form pyridines *(61)*. The conversion of *(59)* into pyrimidine derivatives *(63)* always takes place readily when there is a residue available

[36] The synthesis of glutaconic acid derivatives by this procedure is of little preparative interest, since better methods are available.

Table 9. Aminomethylene compounds $H_2N-CH=CRR'$ *(58)* prepared from active methylene compounds (M) and *s*-triazine *(1)*

(M) R—CH_2—R' R	R'	*(1)* : (M)	Reaction temperature [°C]	Reaction time [hr]	Solvent	Catalyst	Yield [%]	M.p. [°C]
CH_3CO	CH_3CO	1:6	155	0.5	none	none	63	145—146
CH_3CO	CH_3CO	1:1	78	4	ethanol	0.1 mole of AcOH	59	142—144
CN	$COOC_2H_5$	1:3	78	7	ethanol	none	68	134—135
CN	$COOC_2H_5$	1:1	78	0.5	ethanol	0.05 mole of AcOH	98	134.5—135.5
CN	$CONH_2$	1:1	25	4	methanol	0.75 mole of $NaOCH_3$	68	182—183
CN	CN	1:3	25	24	ethanol	none	79 [a]	145—146
CN	CN	2:3	25	0.1	ethanol	none	63 [b]	124—133
CN	CN	1:2	25	0.25	dimethylformamide	none	91	131—138
C_6H_5CO	CN	1:1	25	24	ethanol	none	29 [c]	133—135

[a] Plus 21 % formamidinomethylenemalonodinitrile *(59)*, R = R' = CN.
[b] Plus 37 % formamidinomethylenemalonodinitrile *(59)*, R = R' = CN.
[c] Plus 59 % α,α'-dibenzoylglutaconodinitrile as its formamidine salt *(60)*, R = CN, R' = C_6H_5CO, B = $HC(NH_2)_2$.

in the α-position to the methylene group that can join with the NH_2 group at the other end of the molecule to close the ring. A special case is that of methylene compounds containing an amidine or imido-ether group in the α-position. These lead to the intermediate *(59a)*, which can close the pyrimidine ring by elimination of NH_3 or HX. In both cases, 4, 5-disubstituted pyrimidines [*(63)*, *(63a)*, or *(63b)*] are formed.

These reactions are catalyzed by base. Either *(1)* and its reaction products, *e.g.*, ammonia and formamidine, or added strong bases, *e.g.*, sodium alkoxide, function as condensing agent.

Table 10. Pyridine derivatives prepared from active methylene compounds (M) and *s*-triazine *(1)*

(M) R—CH_2—R' R	R'	*(1)*:(M)	Reaction temp. [°C]	Reaction time [hr]	Solvent	Catalyst	Pyridine derivative	M.p. [°C]	Yield [%]
CH_3CO	$CO_2C_2H_5$	1:3	140	2	none	none	2,6-dimethyl-3,5-diethoxycarbonyl	72—73	50
CN	$C(OC_2H_5)=NH\cdot HCl$	1:1	25	24	ethanol	none	2,6-diethoxy-3,5-dicyano-	144—145	69
CH_3CO	$CO_2C_2H_5$	1:1	78	2	ethanol	1 mole of $NaOC_2H_5$	3-ethoxycarbonyl-4-hydroxy-	228—229.5	26
CH_2CO CO_2-CH_3	CO_2CH_3	1:1	78	0.2	methanol	1 mole of $NaOCH_3$	3,5-dimethoxycarbonyl-4-hydroxy-	262—264	59

In the following, the data available at present [37, 38] are arranged into the classes of compounds that are synthetically accessible by these methods, without regard to mechanistic correlations.

b) *Synthesis of Aminomethylene Compounds*

The first products that can be isolated from the reaction of active methylene compounds with *(1)* are normally aminomethylene compounds *(58)* (Scheme 4). To prevent any further reaction, generally no or, at the most, only a catalytic amount of basic condensing agent is employed. Several examples are collected together in Table 9.

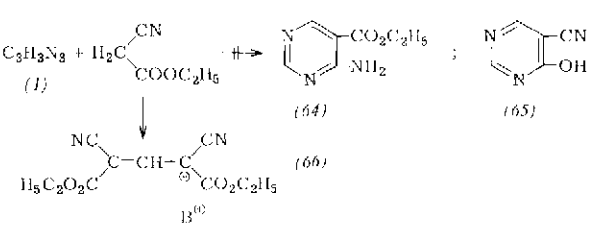
c) *Synthesis of Pyridines*

The material available on the synthesis of pyridine derivatives *(61)* (cf. Table 10) is not extensive enough to allow general conclusions to be drawn. Several of the compounds listed in Table 10 are otherwise only accessible by rather tedious procedures.

d) *Synthesis of Pyrimidines*

The formation of pyrimidine derivatives from *s*-triazine and active methylene compounds frequently proceeds very smoothly and is therefore of great preparative value.

In general, pyrimidines are obtained that are unsubstituted at C-2 and C-6, and hence accessible only with difficulty by other routes. This synthetic method is generally applicable whenever the methylene compound contains at least one substituent in the α-position which



is capable of reacting with an NH_2 group. The behavior of ethyl cyanoacetate is anomalous, because under standard conditions, it does not react with triazine to form the pyrimidine derivatives *(64)* or *(65)*.

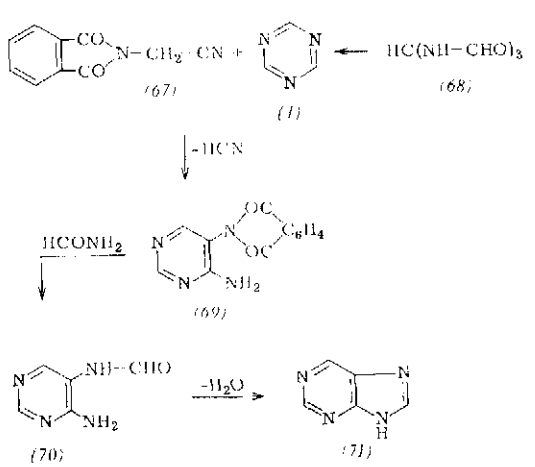
Under more vigorous conditions, the anion of diethyl α,α'-dicyanoglutaconate *(66)*, B = $Na^{\oplus}$ or $H_2N-CH=NH_2^{\oplus}$, is the only product which can be isolated.

[37] *A. Kreutzberger* and *Ch. Grundmann*, J. org. Chemistry *26*, 1121 (1961).

[38] *F. C. Schaefer*, *K. R. Huffman*, and *G. A. Peters*, J. org. Chemistry *27*, 548 (1962); *K. R. Huffman*, *F. C. Schaefer*, and *G. A. Peters*, J. org. Chemistry *27*, 551 (1962).

The pyrimidine synthesis requires a condensing agent, normally a strong base, in stoichiometric amounts. Sodium alkoxides prove to be suitable in all cases except that mentioned above. Exceptions are pyrimidine syntheses with amidines or imido ethers of type *(59a)*, where the hydrochlorides and the free bases condense without a catalyst. Pertinent experimental data are given in Table 11.

The purine synthesis of *Bredereck* [39] from phthalimidoacetonitrile *(67)* and tri(formylamino)methane *(68)* in formamide presumably also belongs to this type of pyrimidine synthesis involving *(1)* and an active methylene compound: *(68)* first reacts to give *(1)* [12], which then condenses with *(67)* as the active methylene compound to form the pyrimidine *(69)*. This intermediate is transacylated by the excess formamide, *e.g.* to give *(70)*, which subsequently cyclizes to form the purine *(71)* in the well-known manner. It is remarkable that yields of 40 % are obtained in these complex reactions.



[39] *H. Bredereck, F. Effenberger*, and *G. Rainer*, Angew. Chem. *73*, 63 (1961).

Table 11. 4,5-Disubstituted pyrimidines *(63)* prepared from active methylene compounds (M) and *s*-triazine *(1)*

R–CH₂–R′ (M) R	R′	*(1)*:(M)	Reaction temperature [°C]	Reaction time [hr]	Solvent	Pyrimidine derivative *(63)* R	R²	Yield [%]	M.p. [°C] or b.p. [°C/mm]
–CN	–CN	1:3	25	24	ethanol	–CN	–NH₂	21 [b]	255–256
–CN	–CN	1:1	78	3	ethanol [d]	–CN	–NH₂	80	255–256
–CN	–CONH₂	1:1	65	0.25	methanol [a]	–CONH₂	–NH₂	55	258–261
–CONH₂	–CONH₂	1:1	78	2	ethanol [a]	–CONH₂	–OH	69	276–278
–CO₂C₂H₅	–CO₂C₂H₅	1:3	160	4	none	–CO₂C₂H₅	–OH	89	194–195
–CO₂C₂H₅	–CO₂C₂H₅	1:1	78	2	ethanol [a]	–CO₂C₂H₅	–OH	42	191–192
–CN	–CSNH₂	1:1	78	2	ethanol [a]	–CN	–SH	90	> 300
–CN	C₆H₅CO–	1:1	78	1.5	ethanol [d]	–CN	–C₆H₅	31	95–96
–CONH₂	–C₆H₅	1:1	78	2	ethanol [a]	–C₆H₅	–OH	46	176–178
–CO₂C₂H₅	C₆H₅CO–	1:2.5	140	2	none	–CO₂C₂H₅	–C₆H₅	30	159–161
–CONH₂	–C(=NH·HCl)–NH₂	1:1	75	1	ethanol acetonitrile [a] 1:1	–CONH₂	–NH₂	72	257–258
–CONH₂	–C(NH)–NH₂	1:1.5	25–65	14	methanol	–CONH₂	–NH₂	53	257–258
–C₆H₅	–C(NH)–NH₂	1:1	25	3	methanol	–C₆H₅	–NH₂	75	152–154
–CO₂C₂H₅	–C(NH)–NH₂·HCl	1:1	80	1.5	acetonitrile	–CO₂C₂H₅	–NH₂	85	102–104
–CO₂C₂H₅	–C(OC₂H₅)=NH	1:1	48–52	24	ethanol [c]	–CO₂C₂H₅	–NH₂	56	102–104
–CN	–C(OC₂H₅)=NH	1:1.5	60–80	0.5	none [c]	–CN	–NH₂	67	250
–CONH₂	–C(OC₂H₅)=NH·HCl	1:0.86	40–50	2	ethanol	–CONH₂	–OC₂H₅	51	138–140
–CO₂C₂H₅	–C(OC₂H₅)=NH·HCl	1:1	20–50	1.5	ethanol	–CO₂C₂H₅	–OC₂H₅	51	25; 82–85/0.1
C₆H₅CO–	–C(OC₂H₅)=NH·HCl	1:1	20–50	1.5	ethanol	C₆H₅CO–	–OC₂H₅	100	67–69
–CN	–C(SCH₃)=NH·HCl	1:1	20–25	3	ethanol	–CN	–SCH₃	64	94,5–96

[a] Contains 1 mole of the corresponding sodium alkoxide.
[b] Plus 79 % of the aminomethylene compound.
[c] Sodium alkoxide replaced by 0.1 mole of acetic acid.
[d] Sodium methoxide.

V. Practical Procedures

s-Triazine from Hydrogen Cyanide via Formimido Ether Hydrochloride [7]

The following procedure avoids the explosively violent reactions occasionally observed by *Pinner* et al. on combining HCN, alcohol, and HCl, and has also proved to be useful in large scale operations (up to 36 moles).

Hydrogen cyanide (108 g), previously dried over $CaCl_2$, is added dropwise at 10–20 °C in the course of one hour, with stirring and with strict exclusion of moisture, to a solution of 150 g of anhydrous HCl in a mixture of 184 g of absolute alcohol and 285 g of absolute ether. Crystallization of ethyl formimido ether hydrochloride begins during the addition of HCN. Effective cooling is required to compensate for the considerable evolution of heat. Stirring is continued for three hours, and the reaction mixture is then allowed to stand overnight. The crystals are filtered off quickly, washed with absolute ether, immediately transferred to a desiccator, and dried over P_2O_5 in an oil-pump vacuum. Yield: 379 g (89 %). The compound is sensitive to moisture.

Next, 40 g of ethyl formimido ether hydrochloride is added in small portions at 10 °C to 68 g of tri-n-butylamine. The mixture is stirred for one hour at room temperature and then distilled at 25 30 mm Hg, the temperature being gradually raised to 110 °C. The distillate consists of ethanol and triazine, and is collected in a flask cooled with Dry Ice. After dilution with petroleum ether and chilling, 7.8 g (79 %) of *s*-triazine crystallizes out.

s-Triazine from Hydrogen Cyanide via 2,4,6-Trichlorohexahydro-*s*-triazine Hydrochloride („Hydrogen Cyanide Sesquihydrochloride") [1, 10, 18]

Freshly distilled anhydrous HCN (50 g) is dissolved in 200 ml of anhydrous ethyl acetate. Anhydrous HCl is then passed through the solution at 10 to 15 °C and with exclusion of moisture until saturation is attained (1.5 hours). After stand-

ing overnight in ice, the mother liquor is decanted from the hard crystal cake. The latter is washed several times with ethyl acetate and immediately freed from excess solvent by drying in a desiccator over P_2O_5 in an oil-pump vacuum. Yield: 140–150 g (92–99 %). The product is sensitive to moisture, although not quite to the same extent as ethyl formimido ether hydrochloride.

The sesquihydrochloride (140 g) is distilled at 20 mm Hg into the water-cooled side-arm of a sausage flask, initially at 120–140 °C and finally at 180 °C (bath temperature). *s*-Triazine sesquihydrochloride, (63–68 g or 81–87 %), condenses in the receiver as a milky, turbid, porcelain-like mass of crystals.

Next, to 90 g of technical grade quinoline there are added in small portions with stirring 63 g of *s*-triazine sesquihydrochloride, and the mixture is slowly heated to 100–110 °C (bath temperature) in an aspirator vacuum. *s*-Triazine is obtained in the receiver, which is cooled with a Dry Ice/acetone mixture, as a colorless, strongly refractive crystalline mass containing only traces of quinoline. M.p. = 84–85 °C. Yield: 27 g (72 %).

s-Triazine from Formamidine [9]

Formamidine hydrochloride (5 g) [40] is heated slowly to 250 °C (bath temperature) in a distillation apparatus at a pressure of 20 mm Hg. Decomposition begins at 120 °C. The triazine is collected in a receiver cooled with a Dry Ice mixture. Yield: 1.2 g (72 %); m.p. = 80–81 °C.

s-Triazine from Tri(formamino)methane [41]

Tri(formamino)methane (58 g) [42] is heated to 160 °C in a round-bottomed flask connected to a distillation apparatus through a 20 cm Vigreux column. After approximately 30 minutes, a clear melt is obtained. The receiver is cooled at –70 °C with Dry Ice/acetone and the reaction mixture distilled at 120–130 °C (oil bath temperature)/70 mm Hg. After any distillable material has been removed, the mixture is again heated for 30 min to 160 °C at normal pressure and the distillation repeated. Alternate heating and distillation are continued until no further *s*-triazine is formed. Yield: 11.5 g (36 %). The crude product is purified by distillation, vacuum sublimation, or recrystallization from ligroin; m.p. = 80 to 81 °C, b.p. = 112–115 °C.

N,N-Di-n-butylformamidine [23]

s-Triazine (4.1 g) is added with ice cooling and shaking to 22.0 g of n-butylamine. The flask is connected to a reflux condenser and slowly heated. The reaction, evidenced by evolution of ammonia, starts already at room temperature. Finally, the flask is heated in a water bath to 80–100 °C until the evolution of ammonia has ceased. The reaction mixture is then distilled *in vacuo*. At 103–104 °C/14 mm Hg *N,N'*-di-n-butylformamidine distills over as a viscous oil with a faint but unpleasant odor of fish. $n_D^{25} = 1.4632$; yield: 22.8 g (97 %).

[40] Preparation from thiourea by desulfurization with Raney nickel in alcohol in the presence of ammonium chloride: *D. J. Brown*, J. appl. Chem. *2*, 202 (1952); *Ch. Grundmann, H. Schroeder*, and *W. Ruske*, Chem. Ber. *87*, 1865 (1954); For the purpose of obtaining *s*-triazine, the preparation of formamidine hydrochloride from hydrogen cyanide is impractical, since the ethyl formimido ether hydrochloride occurring as an intermediate can to much better advantage be converted directly into *s*-triazine.

[41] *H. Bredereck, O. Smerz*, and *R. Gompper*, Chem. Ber. *94*, 1883 (1961).

[42] For the preparation of this compound, see *H. Bredereck, R. Gompper, G. v. Schuh*, and *G. Theilig*, Angew. Chem. *71*, 753 (1959); in *W. Foerst:* Neuere Methoden der präparativen organischen Chemie. Verlag Chemie, Weinheim/Bergstr. 1961, Vol. III, p. 202.

Δ^2-Imidazoline [23]

s-Triazine (3 g) is added to 7 g of ethylenediamine of 98 to 100 % purity. Vigorous reaction starts immediately and is moderated by cooling. The reaction is later completed by heating for two hours at 80 °C. The reaction product distills *in vacuo* as a viscous oil, b.p. = 68–70 °C/3 mm Hg; m.p. 52–55 °C; yield: 7.9 g (97 %). The compound is extremely hygroscopic and readily absorbs carbon dioxide from the air. Picrate, from the components in alcoholic solution: m.p. 201–202 °C.

Theophylline [23]

1.3-Dimethyl-4,5-diaminouracil (1.9 g) [43] and 0.3 g of *s*-triazine are powdered together. The mixture obtained is transferred to a small round-bottomed flask and quickly immersed in an oil bath heated at 180 °C. Reaction starts immediately and is complete within 30 sec. The temperature is maintained for one minute longer at 180–210 °C. The product consists of crude, faintly yellow theophylline, m.p. 256 °C, yield: 99 %. A single recrystallization from water with a little activated charcoal yields the pure product, m.p. 268 °C.

It may be noted for comparison that by *Traube*'s method (boiling with formic acid, then melting at 260–280 °C), a highly impure crude product is obtained in only 80 % yield (m.p. 230–235 °C), which requires several recrystallizations for purification.

Benzoxazole [23]

o-Aminophenol (10.1 g) and *s*-triazine (2.5 g), both finely powdered, are mixed in a small round-bottomed flask equipped with a reflux condenser, and placed in an oil-bath heated at 160–180 °C. Reaction is complete after two hours. Benzoxazole distills over leaving only a trace of residue at 45 °C/4 mm; $n_D^{25} = 1.5560$; yield: 9.8 g (89 %).

1,2,4-Triazole [24]

Finely powdered hydrazine monohydrochloride (20.55 g) is added to a solution of 16.2 g of *s*-triazine in 600 ml of absolute alcohol (freshly distilled over sodium) and the mixture refluxed for eight hours. After cooling, an equal volume of ether is added to complete precipitation of ammonium chloride. The precipitate is filtered off and the filtrate evaporated to dryness *in vacuo*. On recrystallization from chloroform, the residue (21 g) gave pure 1,2,4-triazole, m.p. 120 to 121 °C; yield: 19.7 g (95 %).

3-Amino-1,2,4-triazole [30]

Free aminoguanidine is prepared from its sulfate by allowing the latter to react with an equivalent weight of barium hydroxide in aqueous solution, followed by filtration of the $BaSO_4$ and evaporation of the filtrate under reduced pressure. The crystalline residue rapidly turns red and must therefore be used immediately.

Aminoguanidine (15 g) and *s*-triazine (10.8 g) are mixed in a flask which is placed in an oil bath heated to 210 °C. Reaction sets in immediately with evolution of ammonia. After 30 min, the reaction mixture is cooled, and the brown, viscous resin obtained is dissolved in absolute alcohol. The solution is decolorized with charcoal. After filtration and evaporation, 3-amino-1,2,4-triazole is obtained as a yellowish, microcrystalline powder. After one recrystallization from ethyl acetate, the product melts at 158–159 °C; yield 7.8 g (47 %).

[43] *W. Traube*, Ber. dtsch. chem. Ges. *33*, 3035 (1900).

N^1,N^4-Diphenylformazane [30]

A solution of 4.1 g of *s*-triazine and 32.4 g of freshly distilled phenylhydrazine in 150 ml of absolute alcohol is refluxed for four hours, the color of the solution changing to deep red. After cooling, the solution is poured into open Petri dishes. With protection from dust the samples are left standing for two weeks exposed to air at room temperature. The red color deepens as the solvent slowly evaporates. A mass of red needles finally remains, which is slightly impregnated with an oil; the solid is dried on porous plate. Yield: 28.2 g (84 %). After several recrystallizations, first from aqueous and then from absolute methanol, the diphenylformazane melts at 119–120 °C.

1,2-Diformylhydrazine Dihydrazone [30]

With exclusion of direct light and in a nitrogen atmosphere, 8 g of anhydrous hydrazine is added dropwise to a solution of 4.5 g of *s*-triazine in 50 ml of anhydrous ether. After standing overnight at room temperature, the almost colorless precipitate is filtered off under nitrogen, washed with a small amount of ice-cold anhydrous ether, and dried for two hours in a vacuum desiccator over P_2O_5 in the dark. Yield: 7.7 g (80 %). This product may be used directly for most reactions. It can be purified further by digesting twice for 30 min with 5 ml of ice-cold absolute alcohol and rapid filtration under nitrogen. 1,2-Diformylhydrazine dihydrazone (4.8 g) is then obtained as a pale yellow, microcrystalline powder melting with decomposition at 122–123 °C. In a desiccator over P_2O_5 in the dark, even the purified product is stable for only a few days at the most.

1,2-Diacetyl-1,2-dihydro-1,2,4,5-tetrazine [30]

Crude 1,2-diformylhydrazine dihydrazone (10.5 g) is added in small portions to 40 ml of acetic anhydride and dissolves immediately with evolution of heat. The orange-colored solution is heated for two hours on a steam bath. The excess acetic anhydride is then removed by vacuum distillation, and the residue recrystallized with a small amount of charcoal from 17 ml of hot acetone to yield 3.9 g (26 %) of 1,2-diacetyl-1,2-dihydro-1,2,4,5-tetrazine. After several vacuum sublimations, the product is obtained as pale yellow needles, m.p. 149–150 °C.

2-Phenyl-*s*-triazine [32]

A mixture of 7 g of benzamidine hydrochloride, 4.05 g of *s*-triazine, and 5 ml of methanol is allowed to stand at room temperature. After an hour, formamidine hydrochloride begins to crystallize out and is completely precipitated after 1.5 hours. After standing for 18 hours, the mixture is diluted with 100 ml of water, and 6.8 g (87 %) of 2-phenyl-*s*-triazine precipitate out, m.p. 63–65 °C. The product contains no 2,4-diphenyl-*s*-triazine.

2,4-Dimethyl-*s*-triazine [32]

A methanolic solution of free acetamidine is prepared by treating 28.4 g of acetamidine hydrochloride with 16.2 g of sodium methoxide in 40 ml of methanol, and 4.05 g of *s*-triazine are then added. The mixture is allowed to stand for 18 hours at room temperature. The sodium chloride formed is filtered off and washed with a small amount of methanol. The filtrate is evaporated to dryness *in vacuo* and the distillate collected in a receiver cooled with Dry Ice/acetone. The crude distillate is fractionated at atmospheric pressure to remove methanol. A residue of 5.7 g crude dimethyl-*s*-triazine (84 %), m.p. 36 °C, is then obtained. According to a mass spectroscopic analysis, this contains 82 % dimethyl-*s*-triazine and 8 % methyl-*s*-triazine.

Fractionation of this crude material in a spinning band column yields about 60 % pure 2,4-dimethyl-*s*-triazine, b.p. 134–135 °C, m.p. 46–47 °C [10].

2-Ethyl-*s*-triazine [33]

A mixture of 16.5 g of 72 % ethyl propionimidate containing propionitrile and ethanol as contaminants [44], 6.5 g of *s*-triazine, and 10 ml of ethanol is heated for 4.5 hours to 80 °C. On vacuum distillation, a main fraction of practically pure 2-ethyl-*s*-triazine (4.3 g, 50 % yield, b.p. 50–65 °C/35 mm Hg) is obtained. The bottom fraction consists essentially of 2,4-diethyl-*s*-triazine (0.8 g, b.p. 65 to 80 °C/35 mm Hg).

2-(*m*-Nitrophenyl)-*s*-triazine [33]

A mixture of 8.9 g of ethyl *m*-nitrobenzimidate ether (73 % pure) [33, 45], 3.8 g of *s*-triazine, 0.60 g of glacial acetic acid, and 10 ml of ethanol is refluxed for three hours. On cooling, 7.6 g (82 %) of practically pure 2-(*m*-nitrophenyl)-*s*-triazine crystallizes out; m.p. 127–129 °C after recrystallization from toluene.

3-Aminomethylenepentane-2,4-dione [37]

Acetylacetone (37 g) and *s*-triazine (5 g) are boiled gently (bath temperature 155 °C) for 30 minutes. On cooling, 8.1 g of a brownish-yellow crystalline material precipitates and is filtered off. Additional 6.8 g are obtained when the mother liquor is evaporated *in vacuo* up to a boiling point of 100 °C/16 mm Hg; yield: 63 %. Upon recrystallization from methanol, 3-aminomethylenepentane-2,4-dione is obtained as yellowish scales, m.p. 145–146 °C.

Dimethyl 4-Hydroxypyridine-3,5-dicarboxylate [38]

A solution is prepared from 1.75 g of dimethyl acetonedicarboxylate and 0.55 g of sodium methylate in 15 ml of absolute methanol, 0.80 g of *s*-triazine being then added. After the exothermic reaction has subsided, the solution is refluxed for 10 minutes even though colorless crystals start to precipitate. After cooling, the precipitate is filtered off, washed with water, and recrystallized from glacial acetic acid, 1.25 g (59 %) of dimethyl 4-hydroxypyridine-3,5-dicarboxylate, m.p. 260–262 °C, being obtained.

Ethyl 4-Hydroxypyrimidine-5-carboxylate [37]

A solution of 6 g of *s*-triazine in 35.6 g of diethyl malonate is heated at 160 °C for four hours. The *s*-triazine that sublimes off is removed from the condenser walls from time to time and pushed back into the reaction mixture. On cooling, a yellowish precipitate slowly appears. After it has been allowed to stand for several days, it is filtered off. An additional

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[44] Prepared according to *F. C. Schaefer* and *G. A. Peters*, J. org. Chemistry *26*, 2783 (1961).

[45] *F. C. Schaefer* and *G. A. Peters*, J. org. Chemistry *26*, 412 (1961).

amount of product can be recovered by evaporating the mother liquor *in vacuo*. After washing the solid with ether, 16.5 g (89 %) of crude product is obtained. Several recrystallizations from methanol yield pure ethyl 4-hydroxypyrimidine-5-carboxylate as beautiful, colorless needles, m.p. 194–195 °C.

4-Amino-5-cyanopyrimidine [38]

Solid malonodinitrile (1.65 g), 2.0 g of *s*-triazine, and 0.1 g of sodium methoxide are added quickly to 5 ml of absolute alcohol. The mixture is shaken to complete solution and refluxed for three hours. Crude 4-amino-5-cyanopyrimidine then appears as a brown precipitate. A further 0.4 g can be recovered by leaving the mother liquor standing overnight. Total yield: 80 %. The pure compound is obtained by recrystallization from water. M.p. 255–256 °C.

5-Benzoyl-4-ethoxypyrimidine [38]

s-Triazine (8.1 g) and ethyl benzoylacetimidate hydrochloride (22.8 g) [46] are shaken together in 20 ml of ethanol. A slightly exothermic reaction takes place, and a clear solution is formed. On cooling, a solid yellow crystal cake is formed, which is broken up and filtered, leaving 22.8 g (100 %) of crude 5-benzoyl-4-ethoxypyrimidine. A single recrystallization from ethanol yields colorless needles, m.p. 67–69 °C.

Received, May 29th, 1962 [A 278/95 IE]

[46] *A. Haller*, Bull. Soc. chim. France (2) *48*, 24 (1887).

COMMUNICATIONS

A New Route to the Indazole Series

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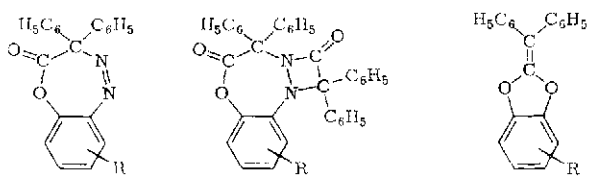
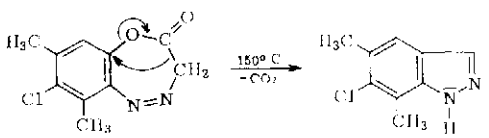
o-Quinone diazides react with ketenes by 1,5-addition with formation of seven-membered ring systems *(1)* [2]. By using an excess of diphenyl ketene, a condensed system *(2)* consisting of a seven- and a four-membered ring is formed. With ketene itself, the reaction stops at the oxadiazepine stage.



(1) *(2)* *(3)*

Although thermal decomposition of *(1)* and *(2)* invariably yields 2-methylene dioxoles *(3)*, the oxadiazepine system *(4)* derived from ketene splits off CO_2 in a slow reaction; the non-planar seven-membered ring system undergoes ring contraction to a planar five-membered ring and is converted into the indazole system *(5)*; colorless needles (from xylene) m.p. 229 °C, are formed in 93 % yield.



(4) *(5)*

The ease of reaction varies with the type of substituents present. In the example given above, the elimination of CO_2 starts only at an elevated temperature, but occasionally the seven-membered ring decomposes spontaneously, and the excess ketene converts the *o*-quinone diazide in one operation into an *N*-acetylated indazole. Thus, *o*-naphthoquinone-2-diazide yields 1-acetyl-4,5-benzoindazole (colorless plates from petroleum ether, m.p. 148 °C).

Received, November 28th, 1962 [Z 489/317 IE]
Publication withheld until now at the author's request.

[1] Part of the Ph. D. Thesis of *R. Dietrich*, Universität Frankfurt a. M., 1962.

[2] *W. Ried* and *R. Dietrich*, Liebigs Ann. Chem., in the press.

9-Borafluorenes

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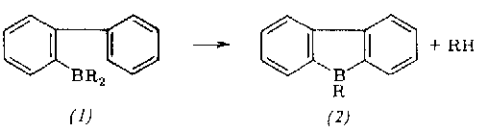
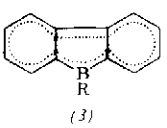
Reaction between 2-biphenylyl-lithium and dialkylchloroboranes gives *B,B*-dialkyl-2-biphenylylboranes *(1)*, which lose alkane at 180–200 °C [1] to give 9-alkylborafluorenes *(2)* in about 65 % yield (R = C_2H_5).



(1) *(2)*

Compounds with larger alkyl groups (*e.g.* propyl, isobutyl) also form alkenes and *B*-monoalkyl biphenylyl boranes as by-products as a result of dehydroboration; the monoalkylbiphenylyl boranes then rearrange to 9-alkylborafluorenes by elimination of H_2, which causes the B–C_{aryl} linkage to be partly hydrogenolysed to form biphenyl (yields: 9-propylborafluorene, 42 %; 9-isobutylborafluorene, 40 %). 2-Biphenylyldiphenylborane does not lose benzene below 280–300 °C, but then it gives 9-phenylborafluorene in 55 % yield.

All 9-borafluorenes with R in position 9 are intensely yellow. This is evidently due to degeneration of the aromatic system caused by the boron atom, so that the compound is best represented by the collective structure *(3)*.

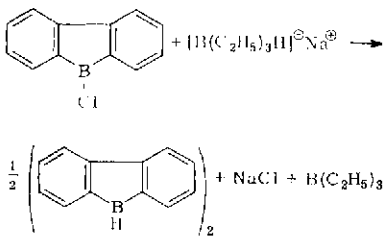


(3)

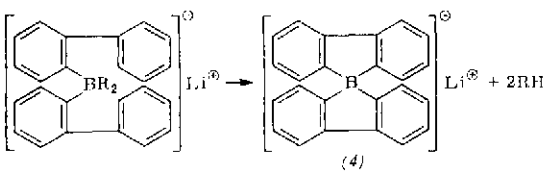
9-Chloroborafluorene, which is also yellow, is obtained smoothly along with alkyl- or aryldichloroboranes by treatment of 9-alkyl- or 9-arylborafluorenes, respectively, with boron trichloride in the presence of BH-compounds [2]. 9-Chloroborafluorene forms colorless etherates. Its diethyl etherate dissociates at 82 °C (m.p.).

Colorless bis-(9-borafluorene), $\nu_{max.}$ (BH_2B) = 1545 cm^{-1}, is obtained from sodium triethylboranate and 9-chloroborafluorene. The material is sparingly soluble in hexane. The compound dissociates into yellow 9-borafluorene ($\nu_{max.}$ (BH) = 2500 cm^{-1}) when its solution in benzene is heated to 80 °C.

As a result of alkyl/aryl exchange [3], 9-alkyl- or 9-arylborafluorenes and triethyl aluminum give dimeric and therefore colorless 9-alkyl- or 9-arylaluminafluorenes [4] (deuterolysis gives monodeuteroalkane or monodeuterobenzene and 2,2'-dideuterobiphenyl) in addition to triethylborane.



The spiro-compound lithium bis-(2,2'-biphenylylidene)-boranate *(4)* is obtained by pyrolysis of 2-biphenyl-lithium and diaryl- or dialkylchloroboranes in molar proportions of 2:1, respectively [5].



(4)

Table 1. 9-Borafluorenes

Compound	B.p. [°C/mm]	M.p. [°C]	Color	ν_{max} [cm^{-1}]
9-Ethylborafluorene	112/0.3	16	yellow	25800
9-Propylborafluorene	130/0.2 [*]	5 [*]	yellow	—
9-Isobutylborafluorene	140/0.2	13.5	yellow	—
9-Phenylborafluorene	180/0.4	118	yellow	24700
Bis-(9-borafluorene)		107	colorless	—
9-Chloroborafluorene	110/0.1	52	yellow	25200

[*] Mixture of n- and isopropyl compounds.

Received, March 21st, 1963 [Z 473/306 IE]

[1] *R. Köster* and *K. Reinert*, Angew. Chem. *71*, 520 (1959).
[2] *R. Köster*, Angew. Chem. *73*, 66 (1961).
[3] *R. Köster* and *G. Bruno*, Liebigs Ann. Chem. *629*, 89 (1960).
[4] *J. J. Eisch* and *V. Kaska*, J. Amer. chem. Soc. *84*, 1501 (1962).
[5] *G. Wittig* and *W. Herwig*, Chem. Ber. *88*, 962 (1955).

Oxidations and Transesterifications of Sugar Derivatives in Dimethyl Sulfoxide

By Prof. Dr. G. Henseke and Dipl.-Chem. G. Hanisch

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der Bergakademie Freiberg/Sachsen (Germany)

During investigations on the partial oxidation of sugars, we obtained 1,2-*O*-isopropylidene-D-glucohexodialdose from 1,2-*O*-isopropylidene-5,6-anhydro-D-glucose. The oxidation occurred with dimethyl sulfoxide in the presence of boron trifluoride [1]. The dicarbonyl sugar was characterized as its phenylhydrazone. Acid hydrolysis led to D-glucohexodialdose which was identified in the form of its bis-phenylhydrazone, m.p. 170–172 °C (decomp.), which was previously obtained by *F. G. Fischer* and *H. Schmidt* [2] in another way.

Oxidation of 1,2-*O*-isopropylidene-6-tosylglucose by a procedure analogous to that of *Kornblum* et al. [3] has not yet succeeded. Instead, transesterification takes place with potassium bicarbonate in dimethyl sulfoxide to give 1,2-*O*-isopropylidene-D-glucosyl-5,6-carbonate, first described by *Haworth* and *Porter* [4].

These oxidation and transesterification reactions in dimethyl sulfoxide can be extended to other sugar derivatives.

Received, March 22nd, 1963 [Z 472/305 IE]

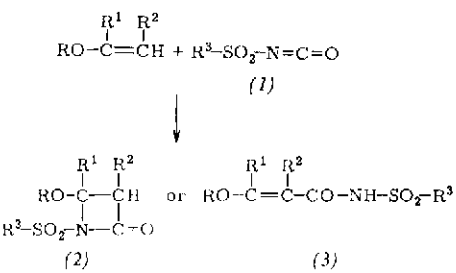
[1] Cf. *T. Cohen* and *T. Tsuji*, J. org. Chemistry *26*, 1681 (1961).
[2] *F. G. Fischer* and *H. Schmidt*, Chem. Ber. *93*, 658 (1960).
[3] *N. Kornblum*, *W. Jones*, and *G. J. Anderson*, J. Amer. chem. Soc. *81*, 4113 (1959).
[4] *W. N. Haworth* and *C. R. Porter*, J. chem. Soc. (London) *1929*, 2796.

The Reaction of Sulfonyl Isocyanates with Vinyl Ethers

By Dr. F. Effenberger and Dipl.-Chem. R. Gleiter

Institut für Organische Chemie und Organisch-chemische Technologie der Technischen Hochschule Stuttgart (Germany)

Sulfonyl isocyanates *(1)* [1], e.g. *p*-toluenesulfonyl isocyanate, react very rapidly and quantitatively with vinyl ethers giving *N*-substituted 4-alkoxyacetidin-2-ones *(2)* or *N*-substituted β-alkoxyacrylamides *(3)*.

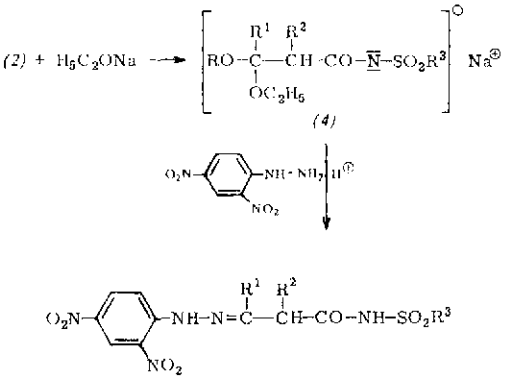


(1)

(2) *(3)*

Substituents R	R^1	R^2	R^3	React. temp. [°C]	Product	M.p. [°C]
C_2H_5	H	H	CH_3–C_6H_4	20	*(2)*	56–63
C_2H_5	H	CH_3	CH_3–C_6H_4	20	*(3)* + *(2)*	—
C_2H_5	H	C_2H_5	CH_3–C_6H_4	20	*(2)*	76–78
C_2H_5	H	C_2H_5	CH_3–C_6H_4	80	*(3)*	—
C_4H_9	H	H	CH_3–C_6H_4	20	*(2)* + *(3)*	—
C_2H_5	H	C_2H_5	Cl	15–17	*(3)*	—
Dihydropyran			CH_3–C_6H_4	20	*(2)* + *(3)*	65–70
Dihydropyran			CH_3–C_6H_4	80	*(3)*	204–205
Dihydropyran			Cl	15–20	*(3)*	88–90

Formation of *(2)* or *(3)* depends on the substituents as well as on the reaction conditions. Viscous oils are often obtained when mixtures of *(2)* and *(3)* are formed, but *(2)* or *(3)* alone is almost always a crystalline compound. The characteristic carbonyl frequency for *(2)* lies between 1780 and 1800 cm^{-1}, for *(3)* between 1670 and 1730 cm^{-1}.



(4)

With sodium ethoxide, *(2)* gives salts of *N*-substituted β,β-dialkoxypropionamides *(4)*, which form hydrazones with 2,4-dinitrophenylhydrazine.

Received, March 26th, 1963 [Z 479/309 IE]

[1] *H. Krzikalla*, German Pat. 817 602 (Oct. 18th, 1951); *R. Graf*, Chem. Ber. *89*, 1071 (1956).

Isothiazoles [1]

By Dr. F. Hübenett and H. D. Hofmann

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The synthesis of isothiazoles by the catalysed reaction of olefins with sulfur dioxide and ammonia [1] also succeeds with substituted olefins. Isothiazole-4-carbonitrile (m.p. 87–88 °C, *ca.* 10 % yield) is obtained from methacrylonitrile, 4-phenylisothiazole (m.p. 36–37 °C, 60–65 %) from α-methylstyrene, and 5-phenylisothiazole (m.p. 44–45 °C) from β-methylstyrene or allylbenzene in yields of 30–40 %. Mixtures of 3-, 4-, and 5-phenylisothiazoles are also formed by decomposition of dibenzoyl peroxide in isothiazole at 100 °C [2]. Phenylisothiazoles are colorless, distillable liquids and have odors reminiscent of benzonitrile.

Whilst n-butenes yield mixtures of 3- and 5-methylisothiazoles [1] under our reaction conditions, probably as a result of a double-bond isomer equilibrium [3], it is likely that with the isomers β-methylstyrene and allylbenzene, this equilibrium lies largely on the side of the former, owing to conjugation effects. Since no 3-phenylisothiazole was observed in this reaction, the sulfur appears to enter at the double bond, and the nitrogen at the allyl position.

We assume that reactive sulfur/nitrogen compounds such as thionyl imide or its isomers [4] are formed first and always attack the olefin in the same manner. A route *via* sulfur heterocycles also appears possible, for it is known [5] that these compounds react with ammonia preferably in one direction to give isothiazoles.

Received, March 25th, 1963 [Z 475/307 IE]

[1] Communication No. 2; Communication No. 1: *F. Hübenett* et al., Angew. Chem. internat. Edit. *1*, 508 (1962).

[2] *S. Goldschmidt* and *M. Minsinger*, Chem. Ber. *87*, 956 (1954).

[3] *F. Asinger:* Chemie und Technologie der Monoolefine. Akademie Verlag Berlin 1957, p. 839.

[4] *M. Goehring* and *J. Messner*, Z. anorg. allg. Chem. *268*, 47 (1952).

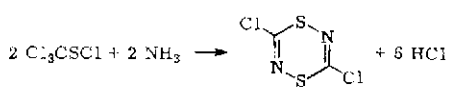
[5] *R. A. Olofson*, Harvard University (1963), personal communication.

3,6-Dichloro-1,4-dithia-2,5-diazine

By Fil. lic. A. Senning

Department of Chemistry, University of Aarhus (Denmark)

Although the reaction between trichloromethanesulfenyl chloride *(1)* and ammonia generally proceeds in an obscure manner and only results in small quantities of nitrogen-free products that have not been identified, reaction in a two-phase system, *viz.* benzene-water, leads to 3,6-dichloro-1,4-dithia-2,5-diazine *(2)*, m.p. 200.5–201.5 °C (from benzene) in 9 % yield.



(1) *(2)*

This colorless crystalline compound is extremely insoluble in common solvents, except benzene. Its elemental analysis, ebullioscopic molecular-weight determinations (in benzene), and its infrared spectrum (which contains very few peaks) agree with the formula $C_2Cl_2N_2S_2$ and the highly symmetrical structure *(2)*.

Received, April 1st, 1963 [Z 482/311 IE]

Preparation of Oxyhalides

By Dr. K. Dehnicke

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Some anhydrous chlorides react with gaseous ozone to form well-defined oxychlorides, *e.g.*

$$TiCl_4 + O_3 \rightarrow TiOCl_2 + O_2 + Cl_2.$$

The reaction is exothermic and complete with respect to O_3 when carried out at the boiling point of $TiCl_4$ (137 °C). Similarly, VO_2Cl can be obtained from $VOCl_3$ and ozone, and $SnOCl_2$ from $SnCl_4$. The resulting oxychlorides are extremely pure.

The reaction using ozone can also be employed for preparing definite oxybromides. The bromides react at room temperature. $TiOBr_2$ is obtained from $TiBr_4$, $SnOBr_2$ from $SnBr_4$, and $V_4O_9Br_2$ from $VOBr_3$. The use of O_3 instead of Cl_2O [1] is especially advantageous for making oxybromides, since no interfering side-reactions can occur [2]. The reaction probably proceeds *via* a halogeno-ozonide, which cannot be isolated.

$$Cl_3Ti{-}O{-}O{-}O{-}TiOCl_2 \rightarrow TiOCl_2 + O_2 + {}^1/_2\,Cl_2.$$

The following example illustrates the practical procedure. $TiCl_4$ is introduced into a three-necked flask fitted with a reflux condenser and an inlet tube, and protected from atmospheric moisture. The O_2/O_3 mixture from the ozonizer is passed through phosphorus pentoxide for drying and then into the boiling $TiCl_4$ until the latter becomes turbid owing to saturation with $TiOCl_2$. At 130 °C, the solubility of $TiOCl_2$ in $TiCl_4$ is 5.6 % by weight [3]. The mixture is cooled, filtered under dry nitrogen, washed repeatedly with CCl_4 or pentane, and dried in a stream of nitrogen or *in vacuo*.

Received, April 3rd, 1963 [Z 478/308 IE]

[1] *K. Dehnicke*, Z. anorg. allg. Chem. *312*, 237 (1961).

[2] *K. Dehnicke*, Angew. Chem. *73*, 763 (1961).

[3] *P. Ehrlich* and *W. Engel*, Z. anorg. allg. Chem. *317*, 21 (1962).

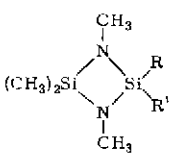
N-Methylcyclosilazanes

By Dr. K. Lienhard and Prof. Dr. E. G. Rochow

Department of Chemistry, Harvard University, Cambridge, Mass. (U.S.A.)

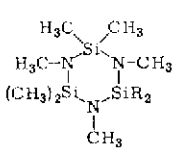
Bis-(*N*-methylamino)dimethylsilane and α,ω-bis-(*N*-methylamino)pentamethyldisilazane [1], obtained from methylamine and dimethyldichlorosilane, react with n-C_4H_9Li or C_6H_5Li to yield $LiN(CH_3)-Si(CH_3)_2-N(CH_3)Li$ *(1)* and $LiN(CH_3)\,Si(CH_3)_2\,N(CH_3)-Si(CH_3)_2-N(CH_3)Li$ *(2)*, respectively. We also found that *(1)* and *(2)* react with chlorosilanes of type $\equiv SiCl_2$ to yield *N*-methylated cyclosilazanes. So far we have prepared the following:

From *(1)*:



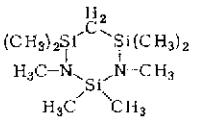
(3) R=R'=CH_3 (B.p. 52–52.5 °C/51 mm; m.p. 16–17 °C; n^{20} = 1.4210)
(4) R=CH_3; R'=C_6H_5 (B.p. 69.5–71 °C/3 mm; n^{20} = 1.4932)
(5) R=R'=C_6H_5 (B.p. 143–144 °C/4 mm; n^{20} = 1.5460)

From *(2)*:



(6) R=CH_3 (B.p. 91 °C/12 mm; m.p. 36 °C) [2]
(7) R=Cl (B.p. 71–72.5 °C/3 mm; m.p. 55–58 °C)
(8) R=C_6H_5 (B.p. 151–152 °C/3 mm; m.p. 62–64 °C)

Compound *(7)* is also formed when two equivalents of *(2)* per equivalent of $SiCl_4$ are employed. Compound *(3)* is converted by catalysts such as NH_4Br into *(6)*, but *(6)* remains unchanged even under more vigorous reaction conditions. Similarly, *(3)* reacts with H_2O and CH_3OH more violently than *(6)* does. The ν_{as}(SiNSi) bands in the infrared spectra of the cyclodisilazanes are displaced by 70–80 cm^{-1} toward lower frequencies compared with those of cyclotrisilazanes. This suggests that the Si–N-bond is weakened because of the decreased bond angle and the consequent lowering of the d_{π}-p_{π} bond contribution.



(9) B.p. 46 °C; m.p. −18 to −17 °C; $n^{20} = 1.4573$

Compound *(9)* was obtained from *(1)* and $Br(CH_3)_2Si-CH_2-Si(CH_3)_2Br$ *(10)*, b.p. 102–103 °C/27 mm [3]. In *(9)*, resonance of the π-electrons of the nitrogen with the d-orbitals of Si – generally assumed to occur in cyclotrisilazanes – is interrupted by the CH_2-group. In spite of this, compound *(9)* is just as stable toward catalytic quantities of NH_4Br as *(6)* is.

In addition to the infrared spectra, the NMR spectra of the above compounds were investigated, and the τ-values of the chemical shifts of the proton-resonance were obtained.

Received, April 5th, 1963 [Z 486/312 IE]

[1] *E. Larsson* and *B. Smith*, Acta chem. scand. *3*, 487 (1949).

[2] Compound *(6)* was first described by *T. W. Ray* and *R. E. Burks, jr.*; cf. Annual Report, Southern Research Institute, Birmingham, Alabama, Feb. 20th, 1961, p. 23.

[3] Compound *(10)* was prepared by condensation of $C_6H_5(CH_3)_2SiCH_2Li$ [obtained according to *G. Fritz* and *H. Burdt*, Z. anorg. allg. Chem. *314*, 51 (1962)] with $C_6H_5(CH_3)_2SiCl$, followed by cleavage of the Si-phenyl bonds with bromine.

Preparation of Metallic Promethium

By Dr. F. Weigel

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Metallic promethium – element 61 – has been obtained for the first time by reduction of PmF_3 *in vacuo*.

"Processed promethium" from the Isotopes Division of Oak Ridge National Laboratory was used as starting material. This substance contained *ca.* 50 curies (approx. 60 mg) of ^{147}Pm together with about 50 mg of Sm, 40 mg of Nd, and about 7 mg of ^{241}Am. The lanthanides were separated on Dowex 50 X 12 by elution with 0.5 M ammonium α-hydroxyisobutyrate at pH 3.5 and 87 °C. The Am was separated by absorption on Dowex 1 X 10 and elution of the Pm with 8 M ammonium thiocyanate. After this separation, the purplish pink solution of Pm^{3+} in HNO_3 still contained about 17 curies of ^{147}Pm, and aliquot portions, each of 100 µl, were removed from it (corresponding to 345 µg of ^{147}Pm each). The purplish pink PmF_3 was precipitated with HF, washed several times with distilled water, centrifuged, and the supernatant solution pipetted off. After drying for 2 days over P_2O_5, the PmF_3 had shrunk together to a compact pellet.

The pellet was transferred to the inner basket of a tantalum crucible system [1, 2], approximately 10 times its weight of pure lithium was placed in the outer crucible; the whole unit was then closed with a tantalum stopper and suspended in the container vessel of a vacuum manifold. At 2.7×10^{-6} mm Hg pressure, the system was heated by means of an induction heater. At 750 °C, excess lithium effused from the crucible system. The crucible was then maintained for periods of 2 mins each at 800 °C, 980 °C, and 1090 °C and then cooled to room temperature over one hour and examined under the microscope. Promethium metal had separated as a solid bead which had fused onto the tantalum wires of the inner container and which had the appearance of a neodymium bead obtained under similar conditions. M.p. 1080 ± 10 °C.

In view of the high radioactivity of the promethium (940 mC/mg), a Berkeley glovebox or a special glovebox for high vacuum operations (so-called 'pianobox') was used.

Received, April 8th, 1963 [Z 480/310 IE

[1] *D. B. McWhan*: Ph. D. Thesis, University of California, Berkeley 1961, Report UCRL-9695 (1962).

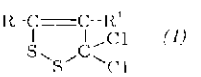
[2] *D. B. McWhan, B. B. Cunningham*, and *J. C. Wallmann*, J. inorg. nuclear Chem. *24*, 1025 (1962).

The 3-Chloro-1,2-dithiolium Cation [1]

By Dipl.-Chem. J. Faust and Prof. Dr. Roland Mayer

Institut für Organische Chemie der Technischen Universität Dresden (Germany)

The compounds obtained by chlorination of 1,2-dithiol-3-thiones [2], or by sulfuration of chloroalkenes [3] were hitherto considered to be 3,3-dichloro-1,2-dithiols (3,3-dichloro-4,5-dithiacyclo-1-pentenes or "dethiodichlorotrithiones") *(1)*. However, they are in fact 3-chloro-1,2-di-

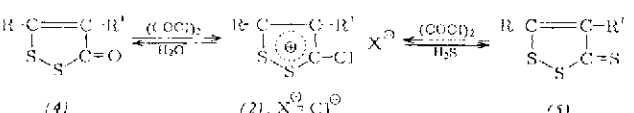


(1)

thiolium chlorides *(2)* and as true salts are very readily soluble in water and almost insoluble in ether, benzene, and hexane. The perchlorates *(3)* are much less soluble in water and are precipitated from ice-cold concentrated solutions of *(2)* by treatment with perchloric acid or ice-cold saturated solutions of sodium perchlorate. The chloride ion of *(2)* is therefore exchangeable.

The chlorine atom in the 3-position of *(2)* is readily substituted by nucleophilic reagents: hot water smoothly converts *(2)* into the dithiol-3-one *(4)*, and H_2S gives rise to the dithiol-3-thione *(5)*.

Dimethylaniline and *(2a)* react on heating to form an already known [4] violet dye (lustrous green perchlorate; decomp. 245–250 °C).



(4) *(2)*, $X^{\ominus} = Cl^{\ominus}$; *(3)*, $X^{\ominus} = ClO_4^{\ominus}$ *(5)*

(a) $R = C_6H_5$; $R' = H$

The 3-chloro-1,2-dithiolium cation is a particularly reactive example of the previously known 1,2-dithiolium ring system. Compound *(2)* is obtained very readily and in good yield by heating dithiol-3-ones *(4)* or dithiol-3-thiones *(5)* with oxalyl chloride in toluene.

Example: 0.1 mole of 5-phenyldithiol-3-one *(4a)*, 25 g of oxalyl chloride (free from phosphorus) and 125 ml of toluene are heated under reflux for 5 hours, carbon monoxide and dioxide being evolved. The yellow needles of *(2a)* which are precipitated are washed with pure benzene; yield 80 %; decomp. 175 to 177 °C. The pale yellow perchlorate *(3a)*, de-

comp. 169 to 173 °C, (recrystallized from a little glacial acetic acid) explodes extremely violently on rapid heating.

Received, April 8th, 1963 [Z 490/316 IE]

[1] Communication No. XXI on Sulfur Heterocycles and their Intermediates; Communication No. XX: *R. Mayer* and *M. Nitzschke*, Chem. Ber., in the press.

[2] *R. Spindt*, *D. Stevens*, and *W. Baldwin*, J. Amer. chem. Soc. *73*, 3693 (1951); *P. Landis* and *L. Hamilton*, J. org. Chemistry *25*, 1742 (1960).

[3] *F. Boberg*, Angew. Chem. *72*, 629 (1960).

[4] *E. Klingsberg* and *A. Schreiber*, J. Amer. chem. Soc. *84*, 2941 (1962).

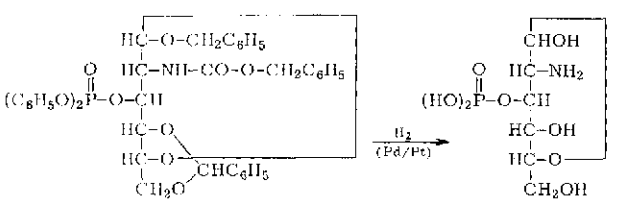
Synthesis of D-Glucosamine-3-phosphate

By Prof. Dr. O. Westphal and Dr. R. Stadtler [1]

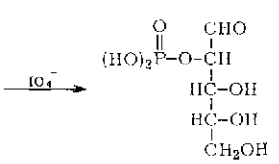
Chemisches Institut der Universität Freiburg i. Br. and Max-Planck-Institut für Immunbiologie, Freiburg-Zähringen (Germany)

D-Glucosamine-4-phosphate has been identified as a unit in the lipoid component (lipoid A) [2] of lipopolysaccharides from Gram-negative bacteria (endotoxin complexes) [3]. Of all the glucosamine phosphates, only the 6-phosphate had previously been identified and synthetized [4], hence we started work upon the synthesis of further glucosamine phosphates and have first prepared the 3-phosphate *(2)*. Benzyl *N*-carbobenzoxyglucosaminide [5] was converted with benzaldehyde/$ZnCl_2$ into benzyl *N*-carbobenzoxy-4,6-*O*-benzylideneglucosaminide, and treatment of this with diphenylphosphonyl chloride in pyridine gave rise to benzyl *N*-carbobenzoxy-3-diphenylphosphoryl-4,6-*O*-benzylideneglucosaminide *(1)* in about 80 % yield. Chromatography on silica gel with 2 % methanol in benzene gave two crystalline fractions, one with $[\alpha]_D^{20} = +37.5°$ and m.p. 98 °C and the other with $[\alpha]_D^{20} = -39.0°$ and m.p. 125 °C (chiefly α- and β-forms).

Without using strong acids, which displace the phosphoric ester group from C-3 to C-6, it was possible to convert *(1)* into *(2)* by hydrogenolysis. Compound *(1)* was first hydrogenated in ethanol at room temperature with Pd-black. Water was then added up to 33 % (vol.) and hydrogenation continued at 50 °C and finally for 0.5 hour at 60 °C after addition of acetic acid to a concentration of 40 %. The resulting crude glucosamine-3-diphenylphosphate was hydrogenated in absolute alcohol with Pt-black at room temperature. Glucosamine-3-phosphate *(2)* was purified by chromatography on cellulose powder with ethanol/water (1:1). We obtained *(2)* in 25–30 % yield, calc. from *(1)*. It was taken up in a very small amount of water, and the solution treated with acetone. Needles of *(2)* crystallized out in the cold, m.p. about 180 °C (decomp.); $[\alpha]_D^{20} = +70 \pm 5°$ (c = 0.03 in water), no mutarotation.



(1) *(2)*



(3)

Acetylation in pyridine/acetic anhydride produced a good yield of crystalline tetraacetate, m.p. 148–150 °C (from ethanol/ether).

High-voltage electrophoresis of *(2)* on paper between pH 3 and 8 showed it to be homogeneous and different from glucosamine-6-phosphate. Degradation of *(2)* with periodate [6] yielded D-arabinose-2-phosphate *(3)*, which behaved on paper chromatography (ethanol/water/acetic acid, 80:15:5) and in high voltage electrophoresis like the degradation product of D-glucose-3-phosphate [7] and which was different from D-arabinose-3-phosphate (obtained by degradation of D-glucose-4-phosphate with periodate [7]) and from arabinose 5-phosphate [3]. In the Elson-Morgan test, *(2)* gives a significantly weaker color reaction as compared to free glucosamine (only about 30 %; the intensity increases on further hydrolysis).

Lambert and *Zilliken* [8] have also synthetized *(2)* independently by a similar route.

Received, April 24th, 1963 [Z 488/315IE]

[1] Part of the Ph.D. thesis of *R. Stadtler*, Universität Freiburg, 1962.

[2] See for example *O. Westphal*, Ann. Inst. Pasteur *98*, 789 (1960).

[3] *A. Nowotny*, *A. Closse*, *O. Lüderitz*, and *O. Westphal*, unpublished observations; see *A. Closse* Ph.D. Thesis, Universität Freiburg, 1962.

[4] *F. Maley* and *H. A. Laroy*, J. Amer. chem. Soc. *78*, 1393 (1956).

[5] *K. Heyes* and *H. Paulsen*, Chem. Ber. *88*, 188 (1955).

[6] *R. Jeanloz* and *E. Forchielli*, Helv. chim. Acta *33*, 1690 (1960).

[7] *P. Szabo* and *L. Szabo*, J. chem. Soc. (London) 3765 (1960).

[8] *R. Lambert* and *F. Zilliken*, Chem. Ber. (1963), in the press.

O-Alkylnitrosoimmonium Salts, a New Class of Compounds

By Prof. Dr. S. Hünig, Dr. L. Geldern [1], and Dr. E. Lücke

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By analogy to the smooth *O*-alkylation of *N,N*-dialkylcarboxamides [2], *N,N*-dialkyl-*N*-nitrosamines react with triethyloxonium fluoroborate [3] in ethylene chloride, or with methyl or ethyl iodide and silver perchlorate in nitromethane to give the immonium salt *(1)* by *O*-alkylation. The salts *(3)–(8)* exhibit a characteristic band at 1540–1575 cm^{-1} which can be attributed to the mesomeric system in *(1)*. The tautomeric form *(2)* is absent because there is no band between 1600 and 1700 cm^{-1} ($>C=\overset{\oplus}{N}<$ [4]) nor between 3050 and 3500 cm^{-1} ($>N-H$). Moreover, proton resonance spectra show that *(4)*, *(5)*, and *(7)* have two equal methylene groups adjacent to the hetero nitrogen atom. The salts dissolve without decomposition even in hydroxylic solvents but evolve nitrogen in strong bases. Salt *(4)* consumes two

Table 1. *O*-Alkylnitrosoimmonium salts

			M.p. [°C]	Infrared absorption [cm^{-1}]	Yield [%]
(3)	$(CH_3)_2N-\overset{\oplus}{N}=O-C_2H_5$	$BF_4^{\ominus}$	36–39	1575	93
(4)	$(CH_2)_4N-\overset{\oplus}{N}=O-C_2H_5$	$BF_4^{\ominus}$	66–67	1570	97
(5)	$(CH_2)_5N-\overset{\oplus}{N}=O-C_2H_5$	$BF_4^{\ominus}$	50.5–51	1562	91
(6)	$(CH_2)_5N-\overset{\oplus}{N}=O-CH_3$	$ClO_4^{\ominus}$	59–61	1560	92
(7)	$(C_6H_5-CH_2)_2N-\overset{\oplus}{N}=O-C_2H_5$	$BF_4^{\ominus}$	oil	1540 [a]	98
(8)	$(C_6H_5-CH_2)_2N-\overset{\oplus}{N}=O-CH_3$	$ClO_4^{\ominus}$	101–102	1540	96

[a] Film, others in Nujol.

moles of hydrogen on hydrogenation with Pt catalysts. *N*-Aminopyrrolidine and ethanol are formed, thereby establishing the *O*-alkylation.

Received, May 2nd, 1963 [Z 495/320 IE]

[1] Results partly from the Diploma Thesis, Universität Marburg, 1960.

[2] *H. Meerwein, W. Florian, N. Schön,* and *G. Stopp,* Liebigs Ann. Chem. *641*, 1 (1961).

[3] *H. Meerwein* et al., J. prakt. Chem. *147*, 257 (1937); *154*, 83 (1940).

[4] *G. Opitz, H. Hellmann,* and *H. W. Schubert,* Liebigs Ann. Chem. *623*, 117 (1959).

The Preparation of Trimethyl-silanolate and -germanolate

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A recent paper [1] has prompted us to report on investigations concerning more advantageous preparations of $(CH_3)_3SiOLi$ *(1)* and $(CH_3)_3GeOLi$ *(2)*. Cleavage of hexamethyldisiloxane and hexamethyldigermoxane [2,3] proceeds readily and quantitatively in diethyl ether to yield MR_4 and *(1)* or *(2)*.

$$R_3MOMR_3 + LiR \rightarrow R_3MOLi + MR_4 \quad (R = CH_3,\ M = Si \text{ or } Ge)$$

Tetrahydrofuran impedes the isolation of the reaction product and leads to impure compounds, *viz.* "colored" solutions [1] of colorless *(1)* or *(2)*. The loss of 50% M (as MR_4) is avoided by cleavage of dimethylpolysiloxanes and dimethylpolygermoxanes of any molecular weight, which in diethyl ether leads to quantitative yields of pure *(1)* or *(2)* according to the equation:

$$(R_2MO)_x + x\ LiR \rightarrow x\ R_3MOLi \quad (R = CH_3,\ M = Si \text{ or } Ge)$$

These reactions can also be applied to the analogous S [4] and Se [5] compounds.

Compounds *(1)* and *(2)* are useful for the synthesis, not only of $(CH_3)_3SiOSn(CH_3)_3$ [6] and $(CH_3)_3SiOGe(CH_3)_3$ [7], but also of $(CH_3)_3GeOSn(CH_3)_3$ *(3)*, which cannot be prepared otherwise [1]. Compound *(3)* is obtained quantitatively from *(2)* and trimethyl-chlorostannane as a colorless liquid, b.p. 51 °C/12 mm (identified by analysis and infrared and NMR spectroscopy). As expected, *(3)* is attacked at the Sn atom by organo-lithium compounds.

Received, May 3rd, 1963 [Z 497/319 IE]

[1] *D. Seyferth* and *D. L. Alleston,* Inorg. Chem. *2*, 418 (1963).

[2] *M. Schmidt* and *I. Ruidisch,* Z. anorg. allg. Chem. *311*, 331 (1961).

[3] *I. Ruidisch* and *M. Schmidt,* Chem. Ber. *96*, 821 (1963).

[4] *I. Ruidisch* and *M. Schmidt,* Chem. Ber., in the press.

[5] *I. Ruidisch* and *M. Schmidt,* J. metallorg. Chem., in the press.

[6] *H. Schmidbaur* and *M. Schmidt,* J. Amer. chem. Soc. *83*, 2963 (1961).

[7] *H. Schmidbaur* and *M. Schmidt,* Chem. Ber. *94*, 1138 (1961).

Lithium Trimethylstannolate

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Solutions in ether of $LiCH_3$ react rapidly and quantitatively with hexamethyldistannoxane at room temperature to yield tetramethyltin and lithium trimethylstannolate *(1)* [1].

$$(CH_3)_3SnOSn(CH_3)_3 + LiCH_3 \rightarrow (CH_3)_4Sn + LiOSn(CH_3)_3 \quad (1)$$

Compound *(1)* is colorless, crystalline, very sensitive to moisture, and is slowly decomposed without melting on heating to 200 °C in a sealed tube. It is readily soluble in organic solvents such as ether, benzene, cyclohexane, and CCl_4; in benzene, it exists as the hexamer, as shown by cryoscopic molecular-weight determinations. It exhibits characteristic bands in the infrared spectrum (Nujol) at 3.35 and 3.45 μ (νCH_3), 7.10 and 8.41 μ (δCH_3), and also at 2.95 μ (ρCH_3). Its NMR spectrum (in CCl_4) shows only one proton signal accompanied by symmetrically arranged "satellites" resulting from H-^{13}C, H-C-^{117}Sn, and H-C-^{119}Sn coupling (τ = 9.76 [ppm] against tetramethylsilane, $J_{H\text{-}^{13}C}$ = 128, $J_{H\text{-}^{117}Sn}$ = 54.0, $J_{H\text{-}^{119}Sn}$ = 56.5 [c/sec]).

Alkylstanno-siloxanes and -germoxanes, some of which have been prepared in the past from alkylchlorostannanes and alkali silanoxides or germanoxides [1–3], can be synthetized from *(1)* and alkylchlorosilanes or -germanes. In this way, for example, *(2)* b.p. 48–49 °C/1.5 mm is obtained in good yield by the reaction:

$$(CH_3)_3SnOLi + (C_2H_5)_3SiCl \rightarrow LiCl + (CH_3)_3SnOSi(C_2H_5)_3 \quad [4] \quad (2)$$

Alkyldistannosiloxanes, such as $(CH_3)_3SnOSi(CH_3)_2OSn(CH_3)_3$ *(3)*, can now be obtained for the first time from *(1)* and $(CH_3)_2SiCl_2$. The structure of *(3)*, a colorless liquid b.p. 77 °C/1 mm, was confirmed by analysis and infrared and NMR spectroscopy (τ_1 = 10.12 [ppm] for $(CH_3)_2Si$ and τ_2 = 9.62 [ppm] for $(CH_3)_3Sn$, $J_{H\text{-}^{117}Sn}$ = 54.7 [c/sec], $J_{H\text{-}^{119}Sn}$ = 57.2 [c/sec]). These NMR data show marked differences from the constants of analogous compounds such as $(CH_3)_3SiOSi(CH_3)_2OSi(CH_3)_3$ with τ = 9.98 for $(CH_3)_3Si$, and $(CH_3)_3SnOSn(CH_3)_3$ with τ = 9.77 [ppm], $J_{H\text{-}^{13}C}$ = 128.9, $J_{H\text{-}^{117}Sn}$ = 53.6, and $J_{H\text{-}^{119}Sn}$ = 56.0 [c/sec].

Received, May 3rd, 1963 [Z 498/318 IE]

[1] Cf. *I. Ruidisch* and *M. Schmidt,* Angew. Chem. *75*, 575 (1963); Angew. Chem. internat. Edit. *2*, 328 (1963).

[2] *H. Schmidbaur* and *M. Schmidt,* Chem. Ber. *94*, 1138 (1961).

[3] *H. Schmidbaur* and *M. Schmidt,* J. Amer. chem. Soc. *84*, 1069 (1962).

[4] NMR spectrum: $(CH_3)_3Sn$: τ = 9.60 [ppm], $J_{H\text{-}^{13}C}$ = 129.3 [c/sec], $J_{H\text{-}^{117}Sn}$ = 54.3, $J_{H\text{-}^{119}Sn}$ = 57.2. $(C_2H_5)_3Si$: A_3B_2 problem with $J/\Delta\tau$ = 0.269. τ_{CH_3} = 9.05 [ppm], τ_{CH_2} = 9.54 [ppm], J_{HCCH} = 8.0 [c/sec]. (Measured in CCl_4; c = 5%, 60 Mcps, 23 °C, tetramethylsilane as internal standard).

Ceramic Materials in Reactor Construction

The Conference took place on November 8th and 9th, 1962 at Baden-Baden (Germany), in conjunction with the Annual General Meeting of the Deutsche Keramische Gesellschaft (German Ceramic Society) as a joint meeting of the Ausschuß für Reaktormetalle (Reactor Metals Committee) of the Deutsche Gesellschaft für Metallkunde (German Metallurgical Society) with the German Ceramic Society.

The discussions were held under the chairmanship of Prof. Dr. *A. Dietzel* of the Max-Planck-Institut für Silikatforschung, Würzburg (Germany), and Prof. Dr. *E. Gebhardt*, of the Max-Planck-Institut für Metallforschung, Stuttgart (Germany).

The reports and discussions made it clear that the importance of ceramic materials is steadily increasing, especially for the construction of power reactors. The aim in plants of this kind is to attain temperatures that are as high as possible, in order to make the reactors economically competitive in comparison with conventional plants for the generation of electric energy. This necessitates the use of ceramic materials, but some problems remain unsolved, especially with regard to fuel elements: these include radiation damage under reactor conditions, escape of fission gases, corrosion problems, and economic production methods [1].

The part of the conference conducted by Prof. *Gebhardt* dealt mainly with uranium oxides and uranium carbide.

H. Bumm, Karlsruhe (Germany), showed that uranium dioxide and uranium monocarbide are being increasingly used in place of metallic uranium. Furthermore, the production of metal-ceramic compositions (cermets) and the combination UO_2/BeO were discussed.

D. Harkort, *G. Honcia*, and *H. G. Kling*, Frankfurt/Main (Germany), studied the physical properties of sintered UO_2 preparations in relation to BeO additions. Specimens with beryllium oxide contents of 5, 10, 15, and 20 % by volume were cold-pressed and sintered at temperatures of up to 1600 °C under hydrogen and attained densities of up to 95 % of the theoretical density. It was found that the thermal conductivity increases with increasing BeO content, *e.g.* to exactly double the value for the thermal conductivity of uranium dioxide for an addition of 20 % BeO by volume. A relationship between the thermal expansion and the amount of BeO added could not be observed, nor does beryllium oxide appear to be soluble in uranium dioxide.

The question was raised, during the discussion, whether the conditions of annealing, *viz.* 1600 °C for one hour, are adequate for establishing equilibrium in this system. Safety precautions were carried out in conformity with the regulations of the AEC, and it was seen that the maximum permissible concentration of 2 µg of beryllium per m^3 of air was not exceeded. The dust filters used were designed for dusts with particle diameters >3 µ. It would be interesting to know whether it is worthwhile increasing the conductivity of uranium dioxide at low temperatures by additions of BeO, since heat transfer in high temperature reactors takes place by radiation.

Studies of particle growth in uranium dioxide preparations by *H. Stehle*, Erlangen (Germany), attain special interest because it is possible to utilize particle growth for indirect temperature determinations and, furthermore, because the escape of fission products from the fuel element may be influenced by particle growth. It was noticed that in sintered UO_2 preparations, large particles grow at the expense of small ones by a thermally activated process; seeding is not involved. The results may be expressed in the form:

$$\bar{D}_t^3 - \bar{D}_o^3 = k_o \cdot e^{-87\,000/RT} \cdot t$$

where $\bar{D}$ is the mean diameter of the particle in µ at time t, and k_o is a constant equal to 0.3×10^{12} – 1.2×10^{12} μ^3/h. The experimental results also show that large pores grow at the expense of small ones.

It was emphasized during the discussion that sintered uranium dioxide is free from intrinsic tensions and, therefore, the observed activation energy of 87 kcal/mole is to be ascribed almost exclusively to the initial step in the grain-boundary shift. It was noticed, too, that particle growth may be influenced by radiation in two directions. On the one hand, it is accelerated by stimulation of the initial steps, while, on the other, the fission products limit the particle sizes and thus may cause delay in particle growth. A rough estimate shows that the total influences of radiation probably leave the final result unchanged.

Sintering of UO_2 was discussed by *N. Müller*, Wolfgang bei Hanau (Germany). Uranium dioxide has a higher melting point (2800 °C) than uranium metal. It does not undergo phase inversion on heating and is therefore preferred as fuel, despite its lower thermal conductivity. Moreover, uranium dioxide powder has to be sintered to form pellets. The specific surface area of the original powder and the density of compressed pellets should be as high as possible for high sintered densities. Finer powders also have considerably smaller pore diameters, and it was shown, in accordance with *Stehle*'s results (see above), that pores with mean diameters of ≈2000 Å disappear on sintering. The final density is apparently reached when the diameter of the remaining pores is too large for shrinkage to take place. In the case of super-stoichiometric sintering, experiments show that a plot of the sintered density against the sintering temperature passes through a maximum at about 1200 °C. If sintering is carried out at higher or lower temperatures, preparations of lower density are obtained. This effect was observed using preparations with O/U ratios of 2.05, 2.12, and 2.21. Oxygen has higher partial pressures at higher temperatures and hence probably delays the sintering process and leads to lower densities. With regard to extraneous admixtures, TiO_2 and V_2O_5 cause higher sintered densities at low temperatures, $Ca(OH)_2$ causes lower ones. To a certain extent, sintering temperature and sintering time are interchangeable variables. All these circumstances have to be balanced out for economic production of uranium dioxide pellets.

The pellets produced by sintering pass through an intricate production process and have to be adjusted to their final dimensions by expensive grinding. The waste amounts to 5–15 %. A search for alternative processes was made with a view to reducing costs. *F. Hofmann*, *H. Kroll*, *B. Liebmann*, and *O. Neumann*, Wolfgang bei Hanau (Germany), examined the possibilities of producing UO_2 fuel elements by vibrational compacting and hammering. A promising idea, that is also particularly suitable for processing mixed uranium/plutonium oxides, which may only be handled with stringent safety precautions, involves preliminary compacting of the powders in a tubular envelope by vibration and subsequent compression to the final density by hammering. The powders have to be carefully prepared for this process by fusing UO_2 in a special smelting plant and subsequent milling. A scrutinizing final check is indispensable after fabrication of the fuel element rods. The thermal conductivity of the preparations obtained by this process is only 35–50 % that of sintered pellets. Subsequent sintering does occur, however, owing to the intense neutron flux in the reactor and, in this way, the

[1] The lectures given have been published in "Berichte der Deutschen Keramischen Gesellschaft" (Reports of the German Ceramic Society) *40*, No. 2 (1963).

thermal conductivity is raised virtually to the level of sintered pellets.

The production and processing of uranium monocarbide for fuel elements was described by *P. Himmelstein*, *B. Liebmann*, and *L. Schäfer*, Wolfgang bei Hanau (Germany).

Uranium monocarbide has a high uranium density and a thermal conductivity exceeding that of uranium dioxide by a factor of 3–6. The preparation was carried out according to the equation:

$$UO_{(2+x)} + (3 + x)C = UC + (2 + x)CO.$$

The original powder had an O/U ratio of 2.00 and a specific surface area of about 0.5 m^2/g. The carbon was incorporated in the form of finely divided natural graphite. The ingredients were thoroughly mixed in a Lödige mixer, the mixture pressed into pellets, and the latter sintered in a vacuum induction furnace at 1700° C. The pellets were subsequently fused in an argon atmosphere in a special arc-type centrifugal casting plant, uranium monocarbide rods of 13 mm ⌀ and 100 mm length being produced by the centrifugal casting process. The rods showed satisfactory uniformity. It was pointed out, in particular, that only about the same number of steps is required for the production of uranium monocarbide as for uranium dioxide. The considerably higher price of the carbide is due to the fact that there is less experience in this field. It could be lowered appreciably if this fuel were required in larger quantities for future reactors.

A survey of less-known uranium compounds and their potential use as nuclear fuels was given by *F. Thümmler*, Stuttgart (Germany). Nitrides, silicides, sulfides, aluminides, beryllides, borides, phosphides, selenides, and tellurides of uranium were discussed. The most important compound of this series is UN, the use of which as a disperse fission material, in conjunction with niobium, molybdenum, stainless steel, and similar metals, is attaining popularity. Furthermore, compounds like US, U_3Si_2, UP, and UAl_2 are of interest. The selenides and tellurides were studied mainly for their thermoelectric properties.

Investigations of the cermet system uranium dioxide/molybdenum were carried out by *E. Gebhardt* and *G. Ondracek*, Stuttgart (Germany). The UO_2/Mo cermet is produced by mixing, cold-pressing, and sintering of the corresponding powders. During the sintering operation, the linear shrinkage was measured; it remains constant with increasing sintering time in the case of pure molybdenum and uranium dioxide, but unexpectedly rises for the cermet samples. It was ascertained by metallographic, X-ray, and electron-microscopic investigations that the reaction

$$3\,UO_2 + Mo = 2\,MoO_3 + 3\,U$$

most probably does not take place during the sintering operation. In contrast to uranium dioxide pellets, the cermet bodies did not show any superficial cracks after irradiation with 10^{16} thermal neutrons per cm^2. With molybdenum additions of between 30 and 50 % by weight, the electrical conductivities of the samples come very close to that of pure molybdenum, which indicates that, from this concentration upwards, the molybdenum forms a continuous basic mass, which can also be seen from the irregular shape of the density curves in this concentration range. Measurements of the thermal expansion showed a decrease of the coefficient of expansion of uranium dioxide with rising molybdenum content. Shaving experiments on the lathe yielded dust-free turnings from uranium dioxide preparations containing additions of molybdenum.

In the discussion, the experimental fact was mentioned that, while the density of pellets increases with rising molybdenum content between 30 and 60 % by weight of molybdenum, the density of the sintered preparations decreases. This phenomenon is explained by assuming the formation of a molybdenum continuum in this concentration range.

[VB 668/83 IE]

SELECTED ABSTRACTS

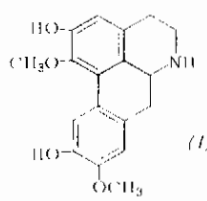
Dialkylaminomethyl thioethers were obtained by *H. Böhme* and *K. Hartke* by treating dialkylaminomethyl halides with thiols or thiophenols in the presence of tertiary amines. The thioethers were resplit by iodine or bromine in indifferent

$$R_2N{-}CH_2{-}Hal + R'{-}SH + NR''_3 \rightarrow R_2N{-}CH_2{-}SR' + [R''_3\overset{\oplus}{N}H]\,Hal^{\ominus}$$

$$2\,R_2N{-}CH_2{-}S{-}R' + I_2 \rightarrow 2\,R_2N{-}CH_2I + R'{-}S{-}S{-}R'$$

solvents at room temperature to form dialkyl or diaryl disulfides together with the corresponding dialkylaminomethyl halides. / Chem. Ber. *96*, 604 (1963) / –Bö. [Rd 526/147 IE]

The constitution of laurelliptine, a new aporphine alkaloid from *Beilschmiedia elliptica* White and Francis (*Lauraceae*), has been elucidated by *P. S. Clezy*, *A. W. Nichol*, and *E. Gellert*. The alkaloid, *(1)*, m.p. 191 °C, $[\alpha]_D^{21} = +47°$ (alcohol),



(1)

forms a dimethyl ether and an *O,O,N*-triacetyl derivative, gives *N*-methyllaurelliptine on hydrogenation with Raney nickel in the presence of formaldehyde, and shows the characteristic ultraviolet absorption of the aporphine alkaloids. *O,O,N*-Trimethyllaurelliptine is identical with glaucine. / Experientia *19*, 1 (1963) / –Ma. [Rd 493/143 IE]

An acid chloride, containing phosphorus and sulfur, with the structure either *(1)* or *(2)*, has been prepared by *M. Becke-Goehring* and *J. Hartenstein* by treating triphosphorus nitrilochloride at 70–80 °C with chlorosulfuric acid. Fission of the triphosphorus nitrilechloride ring leads to a colorless liquid with the formula $PNS_2O_5Cl_4$, which can be vacuum-distilled without decomposition (b.p. 55 °C/0.02 mm, or 63 °C/0.1 mm Hg). In the nuclear magnetic resonance spectrum of the phosphorus, there is a line with a chemical shift of 4 ppm (relative to orthophosphoric acid), indicating the coordination number of 4 for the phosphorus.

$Cl_3P{=}N{-}SO_2{-}O{-}SO_2{-}Cl$ *(1)*

$Cl{-}SO_2{-}N{=}PCl_2{-}O{-}SO_2{-}Cl$ *(2)*

Results of chemical examination support the symmetrical formula *(2)*. / Z. anorg. allg. Chem. *320*, 27 (1963) / Ko. [Rd 532/151 IE]

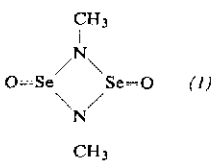
Enrichment of $^{137}Cs^+$ in organisms has been investigated by *K. Pfleger* et al. The ratio Cs^+/K^+ is higher in man than in food by a factor of three. The transport of K^+ and Cs^+ through cell membranes was investigated by incubating rabbit erythrocytes with $^{42}K^+$ and $^{137}Cs^+$. In accordance with the literature, it was found that K^+ is absorbed 4.5 times faster than Cs^+. However, from measurement of the rates of diffusion out of the cells ($K^+/Cs^+ = 1.5$), it must be concluded that, contrary to previous observations, Cs cannot be concentrated in the cells by exchange between serum and the cells. / Experientia *19*, 25 (1963) / –Re. [Rd 497/142 IE]

Determination of the composition of complexes by the continuous variation method of *Job* is made difficult if, in addition to the complex AB_n, one of the components A or B absorbs at the wavelength used for making the measurements. In such a case, a procedure developed by *E. Asmus*, *A. Bull*, and *F. Wollsdorf* can be employed, in which the *Job* mixtures are prepared as usual and their spectra recorded. Mixtures containing more of the (colored) ligand B than corresponds to the composition of the complex, display an isosbestic point. On the other hand, the absorption curves of mixtures with lesser quantities of B do not pass through the isosbestic point. On plotting the extinction coefficient for the wavelength of the isosbestic point against the mole fraction of B, two straight lines are obtained with a point of intersection which gives the composition of the complex. / Z. analyt. Chem. *193*, 81 (1963) / Ko. [Rd 494/139 IE]

Selenylmethylimide *(1)* was prepared by *J. Goubeau* and *U. Weser* from selenium oxychloride and methylamine in methylene chloride at −35 °C:

$$2\ OSeCl_2 + 6\ H_3CNH_2 \rightarrow (OSeNCH_3)_2 + 4\ H_3CNH_3Cl$$

The yield was 12 %. Compound *(1)* is dimeric and forms colorless crystals, m. p. −25 to −23 °C. In the liquid state, on slowly warming to 20 °C, it polymerizes to form a dark red substance, the color being due to elemental selenium which is formed at the same time. When warmed rapidly to 20 °C, *(1)* decomposes explosively to form selenium and amides. The infrared spectrum supports the structure *(1)*.



(1)

/ Z. anorg. allg. Chem. *319*, 276 (1963) / −Ko. [Rd 495/140 IE]

Cadmium acetylides have been prepared by *R. Nast* and *C. Richers*. Diphenylcadmium and phenylacetylene react in ether at room temperature to yield cadmium bis-phenylacetylide, $Cd(C{\equiv}C{-}C_6H_5)_2$, which is found to be insoluble in the common organic solvents. The colorless, crystalline substance is extremely susceptible to hydrolysis. It dissolves easily in liquid ammonia at −34 °C and precipitates out again at −78 °C, as a colorless, crystalline ammoniate. On prolonged warming at 50 °C the ammonia-free phenylacetylide is reformed. The ammoniate can also be obtained from cadmium amide and phenylacetylene or from cadmium thiocyanate and potassium phenylacetylide in liq. NH_3. Reaction of cadmium amide with acetylene in liq. NH_3 results in a solution containing cadmium diacetylide. On evaporation, this yields cadmium carbide CdC_2. When a solution of cadmium thiocyanate in liq. NH_3 is treated with excess potassium hydrogen acetylide or potassium phenylacetylide and barium thiocyanate is then added, the corresponding sparingly soluble barium tetra-alkylcadmiate is formed (R = H or C_6H_5):

$$Cd(SCN)_2 + 4\ KC{\equiv}CR + Ba(SCN)_2 \rightarrow Ba[Cd(C{\equiv}CR)_4] + 4\ KSCN$$

/ Z. anorg. allg. Chem. *319*, 320 (1963) / −Ko. [Rd 496/141 IE]

Gallium oxychloride, GaOCl, has been synthetized for the first time by *P. Hagenmuller* and *A.-M. Hardy*, who used the following three methods:

$$Ga_2O_3 + GaCl_3 \rightarrow 3\ GaOCl$$

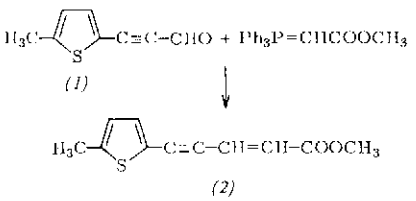
$$3\ GaCl_3 + As_2O_3 \rightarrow 3\ GaOCl + 2\ AsCl_3$$

(both methods: sealed tube technique at 300 °C);

$$Ga_2O_3 + CCl_4 \rightarrow 2\ GaOCl + COCl_2 \text{ at } 150\,^{\circ}C.$$

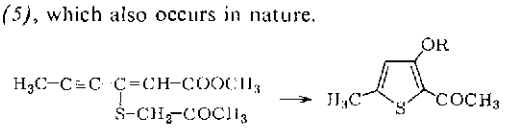
The crystallographic data are: a = 5.653 ± 0.006 Å, b = 8.328 ± 0.004 Å, c = 5.081 ± 0.005 Å; d = 3.32 (meas.) d = 3.37 (calc.); orthorhombic; 4 GaOCl per unit cell. GaOCl, is hygroscopic, is thermally less stable than AlOCl, and decomposes at 410 °C, forming Ga_2O_3 and $GaCl_3$. GaOBr was obtained analogously. / C. R. hebd. Séances Acad. Sci. *256*, 1784 (1963) / −Ma. [Rd 528/150 IE]

The structures and syntheses of new naturally-occurring acetylenic compounds are reported by *F. Bohlmann* and coworkers. The two *cis,trans*-isomers of the ω-(2-methylthien-5-yl)pent-1-en-3-ynoic ester *(2)* (isolated from *Anthemis nobilis* L. [1]) were prepared from 2-methylthien-5-ylpropynal *(1)* by the Wittig reaction:



(1) *(2)*

2-Acetyl-3-hydroxy-5-methylthiophene *(4)*, isolated from *Artemisia arborescens* L., was obtained by intramolecular ester condensation of the keto-ester *(3)*. Methylation afforded its ether *(5)*, which also occurs in nature.



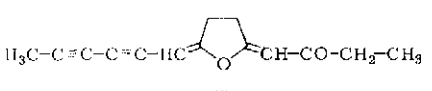
(3) *(4)*, R = H; *(5)*, R = CH_3

The three naturally-occurring thioethers *(6)* (*cis* and *trans*) and *(7)* (*cis*) were prepared by addition of methylthiol onto the corresponding diynes.

$$C_6H_5COC{\equiv}C{-}C{\equiv}CH \rightarrow C_6H_5COC{\equiv}C{-}CH{=}CH{-}SCH_3 \quad (6)$$

$$C_6H_5CH_2C{\equiv}C{-}C{\equiv}CH \rightarrow C_6H_5CH_2C{\equiv}C{-}CH{=}CH{-}SCH_3 \quad (7)$$

In addition to some poly-ynes already known, a compound containing enol-ether and ketone functions was isolated from *Anacyclus radiatus Lois*. On the basis of the results of its degradation and above all on account of its NMR-spectrum, this substance must possess structure *(8)*. Noteworthy is the



(8)

unusually long wavelength of the carbonyl band in its infrared spectrum. / Chem. Ber. *96*, 584, 588 (1963) / −Bm. [Rd 507/146 IE]

Benzoylnitrene (or -azene), $C_6H_5CO\dot{N}$-, which is formed as the primary product of decomposition of benzazide was trapped by *L. Horner* and *A. Christmann* in the form of *S,S*-dimethyl-*N*-benzoylsulfoximine $[(H_3C)_2S(O){-}N{-}CO{-}C_6H_5]$ by irradiating benzazide in dimethyl sulfoxide. The corresponding arylsulfonyl nitrenes formed by photolysis and pyrolysis of sulfonyl azides, afford *N*-sulfonylsulfoximines $[R_2S(O){=}N{-}SO_2{-}R']$ with sulfoxides and *N*-sulfonylsulfimines $(R_2S{=}N{-}SO_2{-}R')$ with sulfides. These nitrenes or azenes are derivatives of univalent nitrogen and are also most probably formed by photolysis and pyrolysis of aryl azides ($\rightarrow Ar{-}\dot{N}$-), in which case the stabilization products are azo-arenes. Thus, for example, about equal parts of 4,4'-dimethoxyazobenzene, azobiphenyl, and 4-methoxy-4'-phenylazobenzene are formed on irradiation of a solution of *p*-methoxyphenyl azide and 4-azidobiphenyl. Arylimenes also give stable products either with reagents which form carbenes or with suitable solvents; thus, on irradiation, 4-azidobiphenyl and 9-diazofluorene form *inter alia* *N*-(9-fluorenylidene)-4-aminobiphenyl, and phenyl azide and glacial acetic acid form *p*-acetamidophenyl acetate and *o*-acetamidophenol. / Chem. Ber. *96*, 388, 399 (1963) / −Ho. [Rd 505/144 IE]

[1] *F. Bohlmann*, *H. Bornowski*, and *H. Schönowsky*, Chem. Ber. *95*, 1733 (1962).

Handbuch der präparativen anorganischen Chemie (Handbook of Preparative Inorganic Chemistry), Vol. I and Vol. II, edited by *G. Brauer*. Ferdinand Enke Verlag, Stuttgart 1960/2. 2nd Edit., Vol. I: XV, 885 pp., 280 figures. Clothbound, price DM 124.– (about $ 31.–); Vol. II: XII, 725 pp. Clothbound, price DM 108.– (about $ 27.–).

The Handbook of Preparative Inorganic Chemistry was reissued in a revised form by *G. Brauer* in 1954 in order to supersede the well-known but out-of-print work of *L. Vanino* in a completely new edition, in the preparation of which *R. Schwarz* has played a considerable part. It has meanwhile been favorably received and has now appeared in a second edition, the first volume having been issued in 1960 and the second volume in 1962.

The basic arrangement has been retained.

A general review of preparative methods is followed by the main part of the book: "Elements and Compounds" and then comes a third part: "Special Classes of Materials" (adsorption and catalytically active substances, salts of hydroxy acids, iso- and heteropolyacids and their salts, carbonyls and nitrosyls, alloys and intermetallic compounds). Nothing has been altered in the fundamental character of the book. The scope has been considerably expanded. The instructions for practical procedures have been brought up-to-date in keeping with scientific developments. The contributers of the individual sections are invariably recognized specialists well established in their respective fields.

The choice of having to consider what material should be reincluded or what may be omitted is, of course, always somewhat subjective. Randomly selected tests have shown the reviewer that apparently a really good and useful selection has been made.

This new edition of the book will be welcomed in both university and industrial laboratories. Thanks are due to the publisher and contributers for the great effort they have put into the preparation of the revised edition. The printing and presentation are excellent; the price is, however, rather high.

W. Klemm [NB 7/44 1E]

Arbeitserinnerungen (Reminiscences of my Work), by *H. Staudinger*. Dr. Alfred Hüthig Verlag, Heidelberg 1961. 1st Edit., XII, 335 pp., 9 figures. Clothbound, price DM 28.– (about $ 7.–).

The book begins with, regrettably, only a brief account of the life of this important pioneer; this is followed by his various investigations on low molecular-weight compounds (60 pages). These are concerned with the expansive fields of interest of *Staudinger*, whose studies on ketene, diazo compounds, flavors, pyrethrum, and the reactions of methylene still captivate the reader of today.

In the second part (over 230 pages), his work in the field of macromolecular chemistry is comprehensively reviewed. The author's lecture on the occasion of his reception of the Nobel Prize for Chemistry on December 11th, 1953 in Stockholm forms the conclusion.

The book contains a good, clear review of the investigations of the *Staudinger* School which is provided with 859 references and which gives an excellent survey of the author's activity. Furthermore, with the mention of former theories, the reader can imagine how controversial opinions were until *Staudinger*'s views prevailed. The individual subjects are discussed in condensed form but complete with references to publications and theses. The book thus gives a good introduction to the problems of macromolecular chemistry, although primarily only for chemists. The book can be warmly recommended to those interested in these topics.

O. Horn [NB 999/43 1E]

Ultrazentrifugenmethoden (Ultracentrifuge Methods) by *H. G. Elias*, Beckman Instruments G.m.b.H., Munich, 2nd Edit. 1961, 219 pp, 41 illustrations, paper, DM 33.– (about $8.50).

Up until 1950, anyone wishing to work with an ultracentrifuge could make do with a single book, *viz.* "The Ultracentrifuge", by *Svedberg-Pedersen*. Nowadays at least two books are necessary; in the first place, "Ultracentrifugation in Biochemistry" by *Schachman*; then, for the theoretical basis, "Mathematical Theory of Sedimentation Analysis," by *Fujita*, and, for the practitioner, this book by *Elias* now universally available. "Ultracentrifuge Methods" contains an abundance of practical advice on all the known techniques. This is particularly valuable to those wishing to acquaint themselves with ultracentrifuge methods in general and to those wishing to use a particular procedure hitherto unfamiliar to them. The text is written in such a comprehensible style that it provides a complete working manual for technical assistants, and does not necessitate supplementary instructional directions. Individual descriptions are given of well-tried methods, and in most cases the limitations of the technique are discussed. Naturally the experienced experimenter will not always follow the methods given here exactly in every detail, but will apply his own suitable variations.

No laboratory employing an ultracentrifuge, no matter what its type or what model it is, should be without this book, which urgently needs a solid cover. *G. Meyerhoff* [NB 13/46 1E]

Encyclopedia of Plant Physiology, edited by *W. Ruhland*, Vol. XII: Plant Respiration, Including Fermentations and Acid Metabolism, Part I and Part II. Springer-Verlag, Berlin-Göttingen-Heidelberg 1960. 1st Edit. Part I: CCLXXX plus 1121 pp., 137 figures, Part II: XX plus 1421 pp., 215 figures. Price (together) DM 598.– (about $ 150.–).

These two volumes of over 2700 pages begin with a detailed biographical appreciation (by *H. Ullrich*) of *Wilhelm Ruhland*, the editor of the Encyclopedia, who died on January 5th, 1960. More than 60 authors give a detailed account of the biochemistry and physiology of biological oxidations, fermentations, energetics, intermediary metabolism, and enzyme chemistry. Higher plants, lower plants, and microorganisms are considered. About half of the contributions are written in English. Two thorough subject indexes (German and English, each about 170 pages) are especially valuable. The authors include many leading scientists from several countries lack of space does not allow them to be mentioned here. The whole work is a monumental achievement. Although some parts will certainly soon be superseded because of the rapid development in this field, the book will remain of great value for many years as a reference work and as an exhaustive account of the present state of this topic.

H. A. Krebs [NB 990/38 1E]

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Principles and Techniques of Diffuse-Reflectance Spectroscopy

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The prerequisites for applicability of the Kubelka-Munk theory of diffuse reflectance for obtaining characteristic color curves of powders are discussed, and some experimental support for the theory is given. Methods are described for eliminating surface reflection, which is always superimposed upon the diffuse reflection and which therefore distorts the spectrum. The effect of interactions with the adsorbent on the reflection spectra of adsorbed molecules is demonstrated by means of examples, and the special suitability of the method for investigating chemisorption and for following reactions at phase boundaries is pointed out. By analogy to the Beer-Lambert law, the Kubelka-Munk function can be used for quantitative photometric analysis. The reflectance curves of white standards are presented, and measurements relating to the conditions for "infinitely thick layers" are reported. The scattering coefficient of the Kubelka-Munk function has been estimated for several samples of color-filters as a function of grain-size and wavelength. The effect of moisture on diffuse reflectance spectra is discussed, and details of the measuring techniques are presented.

1. Test of the Kubelka-Munk Theory

The theory of diffuse reflection and of the transparency of light-scattering and light-absorbing layers has been investigated by numerous authors, since this problem is of great practical significance in many areas (covering power of paints, white content of papers, quality of frosted and ground glass, *etc.*). The most general theory was developed by *Kubelka* and *Munk* [1,2]. The equations derived by other authors proved as a rule to be special cases of the Kubelka-Munk equation [*]. For the special case of an infinitely thick, opaque layer (for practical purposes, with fine powders, this is already achieved at a layer depth of a few millimeters), the Kubelka-Munk equation reads

$$F(R_\infty) \equiv \frac{(1-R_\infty)^2}{2R_\infty} = \frac{k}{s} \qquad (1)$$

where $R_\infty = \Phi_{sample}/\Phi_{standard}$ is the relative diffuse reflectance of such a layer, referred to a non-absorbing standard, *e.g.*, MgO or NaCl, k is the molar absorption coefficient of the sample, defined by Lambert's law $\Phi = \Phi_0 \cdot \exp(-k \cdot d)$, and s is the scattering coefficient, which will provisionally be assumed to be independent of wavelength.

According to Equation (1), a plot of $F(R_\infty)$ as a function of the extinction coefficient k, which is known from transmission measurements, should yield a straight line. This has been confirmed for weakly absorbing materials [5]. Another example of the validity of the Kubelka-Munk function is provided by Figure 1. Here the light absorption of a didymium-glass filter [**] was measured in comparison to a quartz plate of equal thickness, in order to eliminate losses due to surface reflection. The glass was then triturated for several hours in an agate mortar, and the reflectance of the resulting powder measured. For comparison window glass ground in the same manner was used, since the glass matrix of the filter (without the coloring rare-earth ions) was unavailable. Figure 1 shows that the transmittance and reflectance curves can be brought more or less into coincidence by a shift parallel to the ordinate axis [†]. Thus,

[1] *P. Kubelka* and *F. Munk*, Z. techn. Physik *12*, 593 (1931).

[2] *P. Kubelka*, J. opt. Soc. America *38*, 448 (1948).

[*] For a brief summary of the theory and derivation of the Kubelka-Munk function see for instance *Kortüm* [3] and *Kortüm* and *Vogel* [4].

[3] *G. Kortüm*, Rev. univ. Mines Ser. 9, Bd. *15*, S. 495 (1959).

[4] *G. Kortüm* and *J. Vogel*, Z. physik. Chem. N. F. *18*, 110 (1958).

[5] *G. Kortüm* and *H. Schöttler*, Z. Elektrochem. Ber. Bunsenges. physik. Chem. *57*, 353 (1953).

[**] Filter No. BG 36 by Schott and Gen., Mainz (Germany).

[†] Analogous measurements carried out previously by *Schreyer* [3, 6] with the similar color glass BG 20 allegedly yielded appreciably different transmittance and reflectance spectra. Re-examination of these measurements showed that they evidently were incorrect.

measurement of the diffuse reflectance yields a "characteristic color curve" for the investigated material.

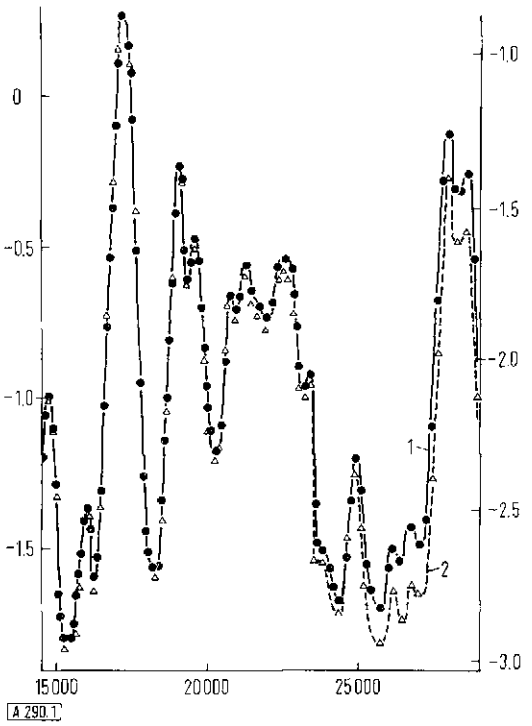

Fig. 1. Transmittance spectrum (Curve 1) and reflectance spectrum (Curve 2) of a didymium-glass filter. The transmittance spectrum was measured relative to quartz glass 0.5 mm thick, the reflectance spectrum relative to powdered colorless glass.

Ordinates: left (Curve 1): log E.
right (Curve 2): log $F(R_\infty)$
Abscissa: Wave number [cm $^{-1}$].

Particularly in the short-wave region of the spectrum, there are small systematic deviations, due essentially to a slight dependence of the scattering coefficient s on wavelength; for further details, see Section 6. These deviations may also be due in part to the fact that the glass matrix of the filter was not available for comparison.

It is important for these measurements that the coloring components in the glass be present in highly dilute concentration. This ensures that, for equal grain-size of the sample and standard, the scattering coefficients will likewise be equal, so that these factors cancel out in comparison measurements, if s is independent of λ. On the other hand, if the sample measured consists of pure absorbents, then the scattering coefficients of sample and standard will generally be different, even when the mean grain-sizes of the two powders are equal, and thus the characteristic color curve obtained will be distorted. The reflection spectrum of the sample would then also become dependent upon the white standard used. Moreover, with pure absorbents, even for finest grain-sizes, a regular (surface) reflection is always observed [7], which adulterates the diffuse reflectance spectrum in proportion to the absorbance of the material.

2. Elimination of Regular Reflection

The regular reflection arising from the plane surfaces of crystallites can be eliminated in two ways:

a) by making measurements between crossed polarizing sheets (Polaroids) or prisms.

b) by diluting the sample with a white standard.

Method a) has already been described in detail [8]. Plane polarized light is used, and care must be taken to ensure that the angle between the plane of incidence and the plane of vibration of the radiation is either 0 ° or 90 °. Under these conditions, regularly reflected light maintains its state of polarization and can be eliminated by an analyzer crossed against the polarizer, while the diffusely reflected light changes its state of polarization and is thus partly transmitted by the analyzer. The polarizing sheets previously employed have the disadvantage of being sufficiently transparent only in the visible region of the spectrum [*]. For this reason, a reflection attachment for the Zeiss spectrophotometer PMQ II was developed in which the polarizer consists of a Glan prism (aperture 7 °), while the analyzer is a shortened Glan-Thompson prism (aperture 30 °) [**]; the attachment extends the range down to about 250 mμ.

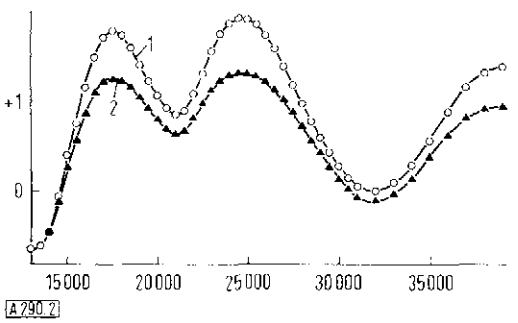

Fig. 2. Reflectance spectra of a chrome alum sample (grain-size about 100 μ) measured relative to CaF_2 with polarized light (Curve 1) and natural light (Curve 2).

Ordinate: log $F(R_\infty)$.
Abscissa: Wave number [cm $^{-1}$].

Figure 2 shows measurements carried out on a sample of chrome alum (grain-size about 100 μ) with this reflection attachment. These were made with CaF_2 as standard, with and without polarizing prisms. Curve 1 shows log $F(R_\infty)$ values obtained using polarized light and lies above Curve 2, obtained with unpolarized light. It can be seen that measurements performed without polarizing prisms (Curve 2) give a spectrum which is depressed by the component of regular reflection the more strongly, the more strongly the material absorbs, since diffuse and regular reflection counteract each other. Strong absorption causes strong regular reflection, but weak diffuse reflection.

In method b) for eliminating regular reflection, the sample is highly diluted with the non-absorbing standard and then measured against the pure standard [9]. At sufficiently high dilution (1 : 10^3 to 1 : 10^5), the regular reflections from the sample and from the standard are approximately equal and, within the limits of experimental accuracy, do not affect the results. This is the case with the color filter mentioned above. Figure 3

[6] *G. Kortüm* and *G. Schreyer*, Z. Naturforsch. *11a*, 1018 (1956).
[7] *G. Kortüm* and *J. Vogel*, Z. physik. Chem. N.F. *18*, 230 (1958).

[*] Recently, polarizing sheets that are transparent in the ultraviolet have also been reported [8].

[**] Obtainable from B. Halle, Berlin-Steglitz (Germany); cf. *G. Kortüm:* Kolorimetrie, Photometric und Spektrometrie. 4th Edit., Springer, Heidelberg 1962, p. 356.

[8] *A. S. Makas*, J. opt. Soc. America *52*, 43 (1962).
[9] *G. Kortüm* and *G. Schreyer*, Angew. Chem. *67*, 694 (1955).

provides an example of the effect of dilution on the reflectance spectrum. Pure anthraquinone was diluted in stages by triturating it in a ball mill with thoroughly

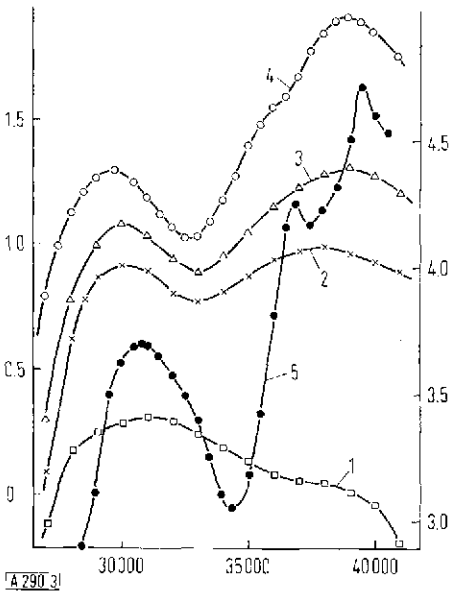

Fig. 3. Reflectance spectra of anthraquinone
(1) undiluted,
(2) adsorbed on NaCl (mole fraction $x = 1.26\times10^{-2}$),
(3) adsorbed on NaCl ($x = 5.0\times10^{-3}$),
(4) adsorbed on NaCl ($x = 1.9\times10^{-4}$).
Curve 5 is the absorption spectrum of a dilute alcoholic solution of anthraquinone.
Ordinates: left (Curves 1—4): log [$F(R_\infty)$/c]; right (Curve 5): log ε.
Abscissa: Wave number [cm^{-1}].

dried NaCl; after each dilution, the reflectance spectrum was measured against pure NaCl as standard. With increasing dilution, the two characteristic bands of anthraquinone at 29600 and 39000 cm^{-1} become increasingly evident. At mole fractions of less than 3×10^{-4}, the spectrum becomes independent of the degree of dilution and is similar to the spectrum in solution. The spectrum therefore approaches that of single molecules adsorbed on the surface of the standard, as can be seen from the fact that an identical spectrum is obtained when the same material is adsorbed by the standard from a dilute solution.

The fact that here the short-wavelength bands of anthraquinone appear so markedly depressed in the spectrum of the pure material is due not only to regular reflection, but probably also to coupling of the π-electron systems of several molecules, if the latter lie in parallel layers along the axis of greatest polarizability. Similar observations were made by *Perkampus* [10] during transmission measurements of thin layers of aromatic materials. This interaction can be eliminated by sufficient dilution.

3. Alteration of Reflectance Spectra of Adsorbed Molecules by Interaction with the Adsorbent

The dilution method is particularly suitable for reflection-spectroscopical investigations, since all uncertainties due to regular reflection or differing grain-size in the sample and standard are practically eliminated. If it is also ensured that the dilution is sufficient (depending on the specific surface area of the white standard, the mole fraction should lie between 10^{-3} and 10^{-5}), so that no complete monomolecular layer of the material under investigation is present on the adsorbent, then the spectrum of the adsorbed single molecule is obtained, and, because of interaction with the adsorbent, this is more or less different from that of the free molecules (in the vaporized state or in inert solvents).

If the adsorption forces are only of the van der Waals type (physical adsorption), then, as a rule, the following differences between the reflectance and the transmittance spectra of a diluted solution are observed: the reflectance spectrum is broadened; the bands are displaced toward longer wavelengths; the vibrational structure, if present at all, is strongly suppressed, frequently appearing only as broad humps. Examples of this are the spectra of anthracene (Fig. 4) and anthraquinone (Fig. 3).

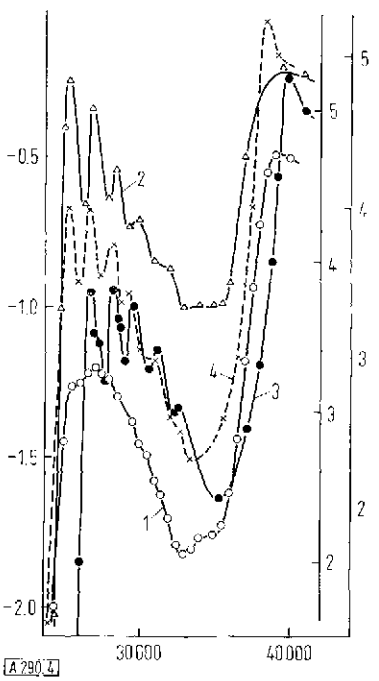

Fig. 4. Reflectance spectra of anthracene adsorbed on anhydrous NaCl (Curve 1) and on NaCl after admission of moisture (Curve 2). Mole fraction of the adsorbed anthracene: $x = 1.42\times10^{-4}$. Curves 3 and 4 show the absorption spectra of alcoholic solutions of anthracene and 9,10-dimethylanthracene, respectively.
Ordinates: left (Curves 1,2): log $F(R_\infty)$; inside right (Curve 3): log ε; outside right (Curve 4): log ε.
Abscissa: Wave number [cm^{-1}].

These effects correspond roughly to the differences due to solvatochromism between spectra in solution and vapor spectra, except that, in general, the former are more pronounced. It is very characteristic that the development of the vibrational structure is highly dependent on whether the surface of the adsorbent is completely dry or whether it contains adsorbed water (Fig. 4). Anthracene adsorbed on absolutely dry NaCl shows hardly any vibrational structure on the p-band; this indicates that the residence time in the excited state is strongly curtailed by the adsorption. When moist air is admitted, the anthracene molecules are evidently displaced from the surface by water, and the vi-

[10] *H. H. Perkampus*, Z. physik. Chem. N.F. *13*, 278 (1957); *19*, 206 (1959).

brational structure emerges again. The p-band of adsorbed anthracene is displaced toward longer wavelengths by about 1200 cm^{-1}, and, thus, has about the same position as the p-band of 9,10-dimethylanthracene in solution; from this it can be concluded that the interaction between the adsorbate and adsorbent is effected primarily at the 9- and 10-positions of the anthracene. With dianthracene, too, the two molecules are likewise attached at C-9 and C-10, and the reflectance spectrum corresponds to the transmission spectrum of *o*-xylene.

In the case of strong interaction between the adsorbent and the adsorbate (chemisorption), which as a rule is due to charge transfer, correspondingly strong changes also occur in the reflectance spectrum compared to that of the free molecules. This has often been discussed in recent years [11–15]. Chemical and photochemical reactions at phase boundaries can likewise be easily followed quantitatively and evaluated kinetically using diffuse-reflectance spectroscopy [16].

4. Photometric Evaluation of the Kubelka-Munk Function

When applying the dilution method, if the molar absorption coefficient k in Equation (1) is replaced by the product $2.30\varepsilon \cdot c$, where ε denotes the extinction coefficient and c represents the molar concentration, then

$$F(R_\infty) \sim \frac{\varepsilon \cdot c}{s} \qquad (2)$$

i.e. at constant external conditions (grain-size, wavelength, temperature, *etc.*), the Kubelka-Munk function is proportional to the molar concentration c, or at sufficiently high dilution also to the mole fraction x of the absorbate; if $F(R_\infty)$ is plotted as a function of c or x, it should yield a straight line passing through the origin. It should therefore be possible to employ Equation (2) for quantitative photometric analysis in the same way as the Beer-Lambert law, remembering that both are limiting laws for sufficiently low concentrations. As an example of the validity of Equation (2) and of the accuracy attainable in photometric determinations of concentration, the function $F(R_\infty)$ of the pyrene band at 29500 cm^{-1} is shown in Figure 5 as a function of the mole fraction x, using dry NaCl as adsorbent. The mean grain-diameter of the NaCl, determined according to the method of *Brunauer, Emmett*, and *Teller* (BET method) was about 1 μ. The curve remains linear up to $x = 2 \times 10^{-4}$ and then falls off. Just at what point it bends away depends critically on the grain-size of the adsorbent; for very fine grains (SiO_2, MgO, etc.), the linear region can extend up to $x \approx 10^{-3}$. The deviation of the curve indicates that the surface of the adsorbent is approaching saturation by the first monomolecular layer. Conversely, the specific surface area of the adsorbent can be determined from this saturation concentration [17]. If the experimental data lying in the linear

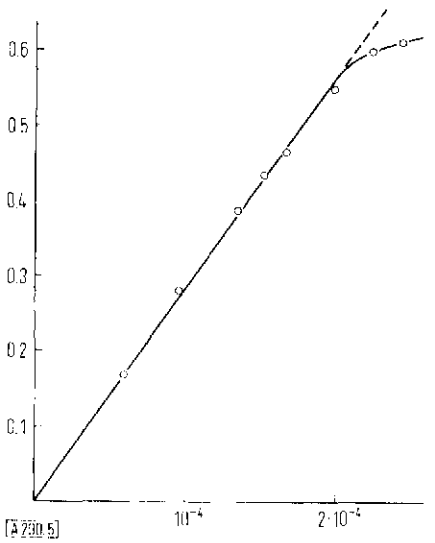

Fig. 5. Kubelka-Munk limiting curve. Dependence of the band intensity of pyrene at 29500 cm^{-1} on the mole fraction. Pyrene in the form of a molecular compound with 1,3,5-trinitrobenzene was adsorbed on anhydrous NaCl (mean grain-size about 1 μ).

Ordinate: $F(R_\infty)$

Abscissa: Mole fraction $\frac{[\text{pyrene}]}{[\text{pyrene}] + [\text{NaCl}]}$

region are reduced up to the concentration $x = 2 \times 10^{-4}$, *i.e.* if, in view of the proportionality of $F(R_\infty)$ and x, the function is multiplied by the appropriate concentration ratio, then the values of $F(R_\infty)$ obtained lie distributed between 0.592 and 0.544. The mean error $\sigma = \sqrt{\frac{\Sigma \delta_i^2}{n-1}}$ of the measurements was 3.2 %; the average deviation of the mean error $\sigma_D = \sigma/n$ was approximately 1.3 %. The mean error depends strongly on the moisture-content of the samples and on the uniformity of distribution of the adsorbate over the adsorbent (duration of grinding). Under favorable conditions, the mean error of photometric determinations may be reduced to 1–2 % [*]. If, even at very low concentrations, deviations from the linear relationship given by Equation (2) are observed, then, as in the case of true deviations from the Beer-Lambert law, this indicates the presence of association or dissociation processes in the surface-boundary phase. Such deviations can be used, for example, to determine the dissociation constants of adsorbed molecular compounds [20].

[11] *G. Kortüm, J. Vogel*, and *W. Braun*, Angew. Chem. *70*, 651 (1958).

[12] *G. Kortüm* and *J. Vogel*, Chem. Ber. *93*, 706 (1960).

[13] *G. Kortüm*, Trans. Faraday Soc. *58*, 1624 (1962).

[14] *G. Kortüm* and *G. Bayer*, Z. physik. Chem. N.F. *33*, 254 (1962).

[15] *G. Kortüm*, and *W. Braun*, Liebigs Ann. Chem. *632*, 104 (1960).

[16] *G. Kortüm, M. Kortüm-Seiler*, and *S. D. Bailey*, J. physic. Chem. *66*, 2439 (1962).

[17] *G. Kortüm* and *D. Oelkrug*, Z. physik. Chem. N. F. *34*, 58 (1962).

[*] For example, photometric determination of concentrations by measurement of diffuse reflectance has been employed for evaluating paper chromatograms [18], and for rutile-anatase analyses [19].

[18] *G. Kortüm* and *J. Vogel*, Angew. Chem. *71*, 451 (1959).

[19] *G. Kortüm* and *G. Herzog*, Z. analyt. Chem. *190*, 239 (1962).

[20] *G. Kortüm* and *W. Braun*, Z. physik. Chem. N.F. *18*, 242 (1958); *28*, 362 (1961).

5. Reflectance of Various White Standards

For purposes of investigating chemical problems by means of reflectance measurements, the white standard must frequently be chosen in such a manner that certain interactions between the adsorbate and adsorbent, *e.g.* acid-base reactions, complex formation, ligand exchange, *etc.*, are either ensured or avoided. It is therefore desirable to measure the reflectance of as many white standards as possible over the whole presently accessible spectrum range, since any significant self-absorption of the white standard will adulterate the reflection spectrum of a sample in the same way as transmission spectra are distorted by self-absorption of the solvent.

There is still no standard available that would provide readily reproducible diffuse reflectance that is greater than about 95 % for the spectral region between 2.5 μ and 200 mμ. Generally, the white standard of best reproducibility is considered to be freshly prepared MgO; its absolute diffuse reflectance has been measured by several authors to an accuracy of about ± 0.5 % [21].

$$R'_{\infty} = \Phi_{\text{incident}}/\Phi_{\text{reflected}} \qquad (3)$$

However, particularly in the ultraviolet region, its reflectance varies with time. The frosted glass standards that are commercially available are constant, but their reflectances decrease sharply above 30000 cm^{-1}. Hence, for our standard, we employed a quartz cuvette with matted windows made of Suprasil®, which was filled with Suprasil powder (grain-diameter ≈ 1 μ) and fused off in an atmosphere of nitrogen [*]. This standard is easy to clean, and, when placed in the same position in the sample holder of the reflection attachment of a Beckman DK2 spectrophotometer, it always gives a constant reflectance. It was standardized once against freshly prepared MgO; the absolute reflectance of the latter (R'_{∞}) obtained by averaging the values given in the literature is reproduced in Figure 6. For wave numbers above 30000 cm^{-1}, for which no values are given in the literature, we arbitrarily assumed a linear decrease from 0.950 at 30000 cm^{-1} to 0.800 at 45000 cm^{-1}. The latter value was chosen such that R'_{∞} did not exceed unity for the materials which reflect best in the ultraviolet region of the spectrum (*e.g.* $MgSO_4$). The values measured against the Suprasil standard were then converted into absolute diffuse reflectances by calculation on the basis of the R'_{∞} values of freshly prepared MgO.

The materials to be measured were generally dehydrated for two hours at the temperatures given in Fig. 6, cooled over P_2O_5 in a desiccator, triturated for two hours in a micro agate ball mill (capacity 50 ml) with a grinding ball of hard metal (tungsten carbide + cobalt) [21a], and then measured immediately. We always employed the purest materials commercially available. The grain-size was determined by means of a measuring microscope. Finer pulverization by prolonged triturating and statistical averaging of the grain-size were deemed unnecessary, since the experimental curves were only to serve for a qualitative appraisal of the reflectance of the white standard in any case. Since these curves still depend on the grain-size, the grain-size distribution, the moisture-content, as well as on the purity and origin of the samples, they generally cannot be reproduced quantitatively.

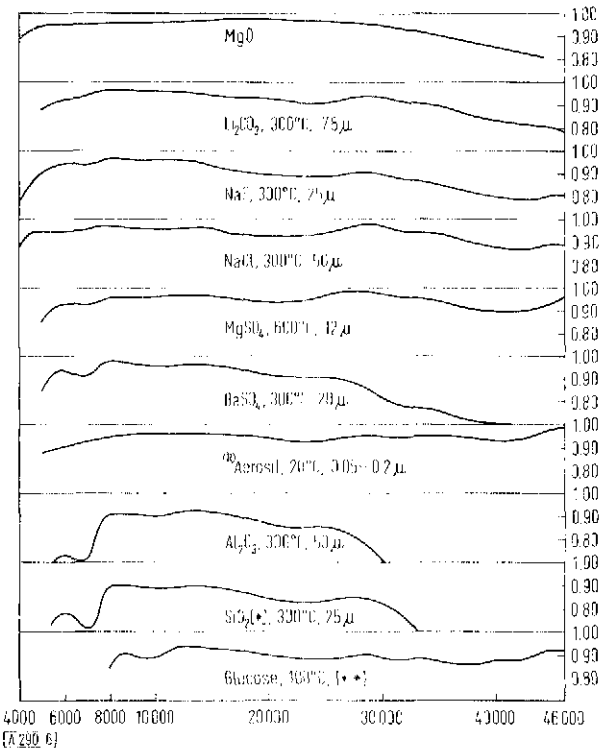

Fig. 6. Dependence on wavelength of the absolute diffuse reflectance of several white standards (maximum grain-size in μ) referred to that of freshly prepared MgO (uppermost curve). The temperatures given are drying temperatures.

[*] Silica gel.

[**] Grain-size not measured.

Ordinate: Absolute diffuse reflectance R'_{∞}.

Abscissa: Wave number [cm^{-1}].

The curves for the most important materials are presented in Figure 6. The data are absolute values calculated by means of Equation (4). The experimental error is ± 2 %.

$$R'_{\infty\,\text{sample}} = \frac{R_{\infty\,\text{sample}}}{R_{\infty\,\text{suprasil}}} \cdot \frac{R_{\infty\,\text{suprasil}}}{R_{\infty\,\text{MgO}}} \cdot R'_{\infty\,\text{MgO}} \qquad (4)$$

KCl, KBr, and CaF_2 behave in a manner similar to NaCl. KI frequently contains traces of elementary iodine, and must therefore always be recrystallized with complete exclusion of air. The reflectance of freshly precipitated $BaSO_4$ in the short-wave ultraviolet region is appreciably better than that shown in Figure 6. The low reflectance of silica gel and Al_2O_3 above 30000 cm^{-1} is remarkable and is probably due to impurities, since Aerosil [*], for example, possesses excellent reflectance. Aerosil is obtainable in various grain-sizes, and thus may well serve as a standard for certain purposes [22]. Since the curves obtained are referred to the measured absolute reflectance of freshly prepared MgO, they may, in some measure, deviate from the true curves in the short-wave ultraviolet region.

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[21] Cf., for example, *F. Benford* et al., J. opt. Soc. America *38*, 445 (1948); *W. E. K. Middleton* and *C. L. Sanders*, ibid. *41*, 419 (1951); *C. L. Sanders* and *W. E. K. Middleton*, ibid. *43*, 58 (1953); *J. T. Gier* et al., ibid. *44*, 558 (1954); *P. A. Tellex* and *J. R. Waldron*, ibid. *45*, 19 (1955).

[*] Produced by Heraeus Quarzschmelze, Hanau (Germany).

[21a] Mfd. by Alfred Fritsch, Idar-Oberstein (Germany).

[*] Aerosil® chemically pure silica gel. Supplier: Degussa, Rheinfelden (Germany).

[22] Cf. *G. Kortüm* and *H. Koffer*, Ber. Bunsenges. physik. Chem. 67, 67 (1963).

Following these measurements, we investigated how thick the sample must be in order to satisfy the condition of infinite layer thickness which entered into the derivation of Equation (1). This can be tested easily by measuring the reflectance R of the layer of desired thickness of the sample in question with a strongly absorbing background (soot, black velvet) and comparing it to that of the same powder with a non-absorbing background (*e.g.* metallic mirror). If R is appreciably different from unity, the layer still transmits radiation. This test was carried out with Aerosil powders of various grain-size, which had a rather narrow grain-size distribution [23]. The surface areas of three samples as determined by the BET method were 38, 106, and 376 m^2/g. Since Aerosils have no "internal surfaces" (pores, *etc.*), the mean grain-size is inversely proportional to the surface area determined by the BET method. A layer thickness of 1 cm was chosen. The measurements established that the samples of coarsest grain (surface 38 m^2/g, grain-size 500–2000 Å) are opaque up to a wavelength of 2.4 μ, while finer samples with grain-sizes of 140 to 560 Å and 50 to 200 Å begin to transmit at 1 and 0.7 μ, respectively. At 2.4 μ, R is only 92 % and 70 %, respectively. This corresponds to the well known greater penetrability of long-wave radiation through scattering media (infrared photography). Thus, for measurements in the short-wave infrared region and for very fine-grain powders, the layer thickness must be increased to 1 cm or more if the Kubelka-Munk function is to be applied.

6. The Scattering Coefficient

In the derivation of the Kubelka-Munk function [Equation (1)], monochromatic radiation is assumed. The theory therefore says nothing concerning the dependence on wavelength of the scattering coefficient s defined by Equation (1). Furthermore, since we are dealing with multiple scattering from closely packed particles of different forms and sizes, no theoretical predictions concerning this dependence are possible. The theory of *Mie* [24] concerning the scattering of a planar wave from isotropic spheres at great distances apart is restricted to single scattering and cannot be applied directly to the present problem [25]. However, the wavelength dependence can be estimated experimentally from the Kubelka-Munk function, if the related values of k are available from transmission measurements: Here it is essential that the spectra be not altered by interactions due to solvation or adsorption. This is for instance the case for the glass filter BG 36 mentioned above. In order to obtain the dependence of the scattering coefficient on mean grain-size simultaneously, we prepared four samples by varying the duration of triturating for 1, 2, 4, and 14 hours, respectively. These were then placed in the thinnest possible layers under the measuring microscope, photographed, and at least 500 particles in each sample were measured. From the data, the mean grain-size [*] was calculated using Equation (5) [26]:

$$\sqrt{\overline{d^2}} = \sqrt{\frac{\sum_i \overline{n_i}\, d_i^2}{\sum_i \overline{n_i}}} \qquad (5)$$

where n_i – the number and d_i – the diameter of the particles. The following are the mean grain-sizes obtained for the four samples:

Sample 1: $\sqrt{\overline{d^2}} = 4.2\,\mu$; Sample 2: $\sqrt{\overline{d^2}} = 2.4\,\mu$;

Sample 3: $\sqrt{\overline{d^2}} = 1.5\,\mu$; Sample 4: $\sqrt{\overline{d^2}} = 1.1\,\mu$.

Figure 6a shows the distribution of grain-size of the most finely divided sample 4. The other more coarse samples had similar distribution curves with maxima being lower and broader.

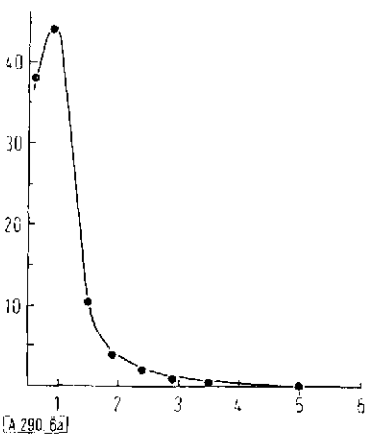


Fig. 6a. Distribution of grain-size of triturated didymium-glass filter (sample 4, $\sqrt{\overline{d^2}} = 1.1\,\mu$). Below 1 μ the microscopic determination of size-distribution is no longer possible.
Ordinate: $(N_i/N)\cdot 100$ [%].
Abscissa: $\sqrt{\overline{d^2}}$ [μ].

The reflectance spectra of the four samples, measured against the same standard (MgO) under identical conditions, are shown in Figure 7.

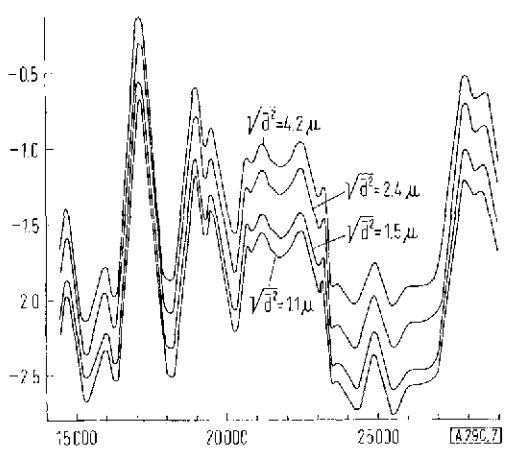


Fig. 7. Effect of grain-size (root-mean-square grain-diameter) on the reflectance spectrum of a pulverized didymium-glass filter, measured against MgO.
Ordinate: log $F(R_\infty)$.
Abscissa: Wave number [cm $^{-1}$].

[23] *E. Wagner* and *H. Brünner*, Angew. Chem. *72*, 744 (1960).

[24] *G. Mie*, Ann. Physik *25*, 377 (1908).

[25] In this connection, cf. *W. Jaenicke*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *60*, 163 (1956).

[*] For simplicity, the expression "mean grain-size" will be used instead of the more cumbersome but correct expression "root-mean-square grain-diameter".

[26] Cf. *G. Kortüm* and *P. Haug*, Z. Naturforsch. *8a*, 372 (1953).

The spectral bandwidth was 18 cm^{-1} for the transmission measurements; by amplifying the photocurrent, this same bandwidth was maintained in the reflectance measurements, and, between 14000 and 28000 cm^{-1}, it did not fluctuate. The measurements were made with a Zeiss PMQ II spectrophotometer equipped with an RA 2 reflection attachment [27].

The scattering coefficient s calculated from these reflectance readings and the k-values obtained from transmission measurements was found to be inversely proportional to the mean grain-size (Fig. 8), confirming previous observations [26].

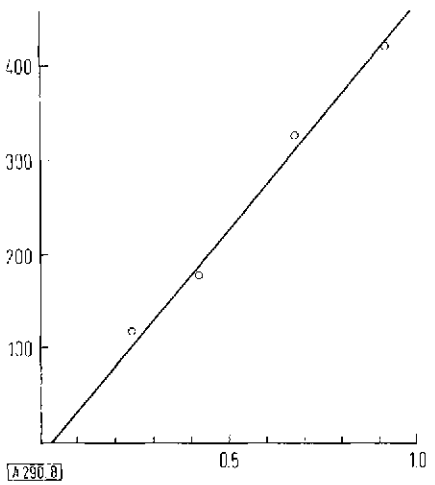


Fig. 8. Dependence of the scattering coefficient on grain-size, measured on the four samples described in Figure 7.
Ordinate: Scattering coefficient, s [cm^{-1}].
Abscissa: $1/\sqrt{\bar{d}^2}$ [d in μ].

The dependence on wavelength of the scattering coefficient s is shown in Figure 9 for various mean grain-sizes. It can be seen that, for coarse-grain powders, s is practically independent of wavelength in the visible region,

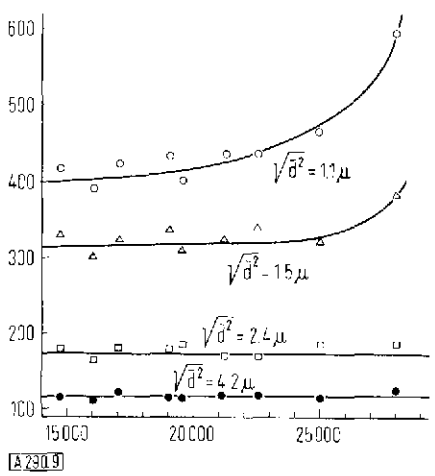


Fig. 9. Dependence of the scattering coefficient on wavelength, for various grain-sizes. Measured on the four samples described in Figure 7.
Ordinate: Scattering coefficient, s [cm^{-1}].
Abscissa: Wave number [cm^{-1}].

as was provisionally assumed above. With the finer powders, a distinct increase in the scattering coefficient is observed at higher wave numbers, although here the mean error of the data is quite naturally much greater. This dependence of the scattering coefficient on wavelength evidently implies a distortion of the short-wavelength spectra obtained from the Kubelka-Munk function on assumption of constant s; however, this distortion is not very great, as can be seen from Fig. 1.

7. Effect of Moisture on Reflectance Spectra

As is evident from Figure 4, the reflectance spectrum of an adsorbed material (*e.g.* anthracene on NaCl) is strongly altered by moisture, not only in its vibrational structure, but also in intensity. In the example illustrated in Figure 4, this is due to displacement of the adsorbate from the surface by water molecules. This phenomenon was also observed in other cases [11, 12]; dipole forces and hydrogen bonds are probably involved here. However, even when such displacements are excluded or are very unlikely, it is frequently noted that on admission of moisture, the samples appear darker; this is also true with pure substances. Since it was to be expected that such effects should depend on whether the material is sparingly or highly soluble in water, we carried out several experiments with K_2CrO_4 and Cr_2O_3 as samples and NaCl and CaF_2 as standards.

The samples and standards were carefully dried and measured with complete exclusion of air. The quartz covering plate was then carefully withdrawn, the sample exposed to an atmosphere of constant humidity, covered again after a while,

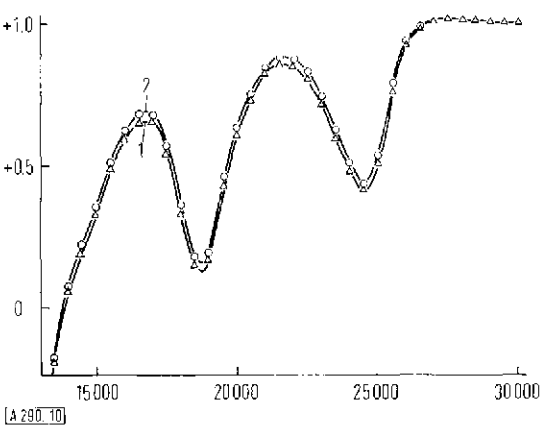


Fig. 10. Reflectance spectra of Cr_2O_3 measured relative to NaCl. Curve 1: anhydrous material; Curve 2: Cr_2O_3, exposed for 24 hours to an atmosphere saturated with water vapor at room temperature.
Ordinate: log $F(R_\infty)$.
Abscissa: Wave number [cm^{-1}].

and measured once more. It was found that the spectrum of pure Cr_2O_3, measured against dry NaCl as standard, remains virtually unchanged when the sample is exposed for 24 hours to an atmosphere saturated with water vapor at room temperature (Fig. 10). On the other hand, the absorption of pure K_2CrO_4 is greatly increased under the same conditions (Fig. 11).

When mixed with the sparingly water-soluble standard CaF_2 and subjected to prolonged treatment with water-saturated air Cr_2O_3 shows a detectable change in its spectrum. This can be practically reversed by storing the sample over P_2O_5 *in vacuo* (Fig. 12). The mixture K_2CrO_4/CaF_2 also shows an increase in absorption if the dry sample is exposed to an atmosphere containing water vapor; this change, however, is irreversible.

[27] For further information, see *G. Kortüm:* Kolorimetrie, Photometric und Spektrometrie. 4th Edit., Springer-Verlag, Heidelberg 1962.

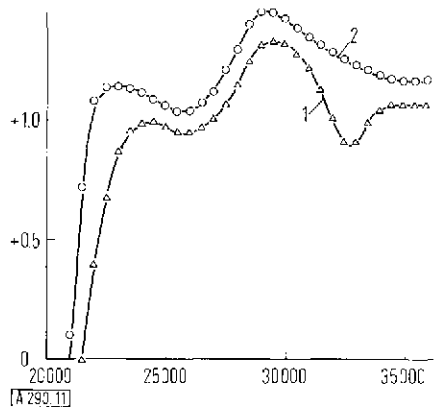


Fig. 11. Reflectance spectra of K_2CrO_4 measured relative to NaCl. Curve 1: anhydrous material; Curve 2: K_2CrO_4, exposed for 24 hours to an atmosphere saturated with water vapor at room temperature.
Ordinate: log $F(R_\infty)$.
Abscissa: Wave number [cm^{-1}].

When mixed with the highly soluble standard NaCl, both Cr_2O_3 and K_2CrO_4 show appreciable elevation of the bands even after being kept for only an hour over 40% H_2SO_4 ($p_{H_2O} \approx 11$ mm Hg); this can be reversed only to a slight extent by subsequent storage over P_2O_5 *in vacuo*.

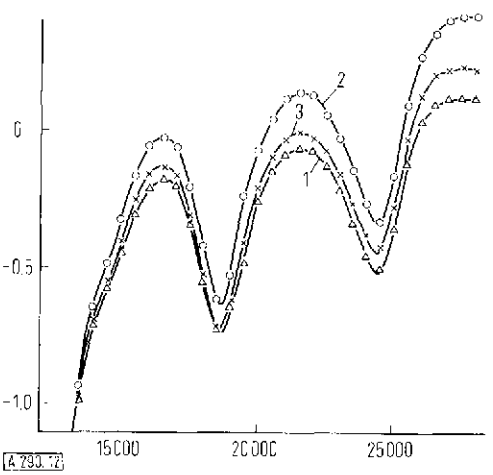


Fig. 12. Reflectance spectra of a mixture of Cr_2O_3 and CaF_2 ($c_{Cr_2O_3} = 0.902$ mole/l) measured relative to CaF_2. Curve 1: anhydrous material; Curve 2: after exposure for 72 hours to air saturated with water vapor; Curve 3: After 7 days over P_2O_5 *in vacuo*.
Ordinate: log $F(R_\infty)$.
Abscissa: Wave number [cm^{-1}].

These observations can be interpreted as follows. If the powders under examination are difficultly soluble in water, as Cr_2O_3 and CaF_2 are, the only effect of the water is evidently condensation in the pores of the powder and partial displacement of the air present there. Since the scattering coefficient depends on the ratio of the refractive indices of the sample and the surrounding medium, and since this ratio is decreased by the penetration of the water, the scattering coefficient is decreased; thus, according to Equation (1), $F(R_\infty)$ is increased. This effect must be largely reversible, as is in fact observed with pure Cr_2O_3 and $Cr_2O_3 + CaF_2$. The observation that the change in the spectrum cannot be completely reversed may be due to the fact that the condensed water is extremely difficult to remove from the finest pores.

With water-soluble powders such as K_2CrO_4 and K_2CrO_4 + NaCl, additional recrystallization effects are encountered which lead to an increase in grain-size and thus to increased absorption as a result of the greater depth of penetration of the radiation [4]. These effects naturally cannot be reversed by subsequent drying; moreover, they should be much larger than the effects mentioned before. Superficially, this recrystallization can sometimes be recognized merely from the observation that a powder that was originally packed loosely into the measuring cell contracts to a hard cake under the influence of moist air. Independent of this, the addition of water vapor can naturally lead to reactions at the phase boundary (hydration of ions, shifts of chemisorption equilibria, *etc.*), which may lead to additional sharp changes in the spectrum, as already indicated. In general, the use of water-insoluble standards is recommended, if this is not ruled out for other reasons. It is generally preferable to work with complete exclusion of moisture; this, however, calls for appreciably greater experimental expenditure.

8. Details of Measuring Techniques

Commercially available spectrophotometers are generally provided with a special attachment for making diffuse reflection measurements [27], either for direct or for diffuse irradiation over an integrating sphere. In the latter case, the conditions of irradiation must be the same for both sample and standard, since otherwise a "spherical error" is introduced, which can become very appreciable [27].

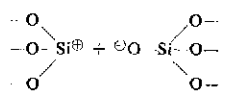
The essential difficulty involved in the measurements consists in the preparation of reproducible samples with uniformly flat surfaces and identical packing densities. To achieve this, the powder to be measured is loosely heaped into the sample cell and then compressed with a polished, carefully dried metal stamp that fits exactly into the cell. Alternatively, the powder can also be covered with a piece of glazed paper and rolled flat with a glass rod.

The preparation of absolutely anhydrous samples has already been described in detail [11]. It is an elaborate process that must be carried out with extreme care, since moisture can strongly affect the results of the measurements, as noted earlier. If we are dealing with comparative or quantitative photometric measurements, the process of triturating in a ball mill that serves to dilute the samples with the white standard should also be standardized, if possible; porcelain mortars of 250 ml content with two large or six small porcelain balls have been found suitable for this purpose. If the material to be ground is hard, agate mortars with agate or hard-metal balls (tungsten carbide + cobalt) are to be preferred. Within a given series of measurements, the same kind of mortars with the same balls should always be employed if the measurements are to be quantitatively reproducible. The grain-size of the ground material depends essentially on the kind and number of grinding balls. Even the number of revolutions of the ball mill should be kept carefully constant within a given series of measurements; the same holds true for the duration of triturating. The standard must be prepared and handled in the same manner as the sample. The duration of grinding differs from case to case, depending on the hardness and the desired purpose of the ground material. To obtain uniform adsorption of the material under investigation on the surface of the standard, grinding should

be continued for at least six hours, preferably overnight. In order to achieve the finest possible grain, 12–14 hours are required; further grinding is usually of no advantage, since the finest grains ultimately recoalesce, and an equilibrium in respect to grain-size and grain-size distribution is attained. During long grinding periods, slight abrasion of the mortars and balls cannot be avoided. Systematic investigation has shown that this abrasion does not affect the measurements within the accuracy of the method; the $F(R_\infty)$ values remain constant to within 1–2% if the grinding period is prolonged beyond the time required to attain equilibrium.

In choosing the standard for diluting the sample, care must be taken that the latter does not react with the standard. Thus, acids adsorbed on MgO or carbonates yielded the spectrum of the corresponding salts; conversely, any salts adsorbed on acidic Al_2O_3 showed the superimposed spectrum of salt and acid. The presence of moisture has various effects, since hydration of ions on the surface can also occasion additional changes in the spectrum.

Certain standards cannot be used in a highly dried state for the adsorption of organic materials. Thus, for example, even after drying for only an hour at 600 °C, silica gel becomes so active that, during the grinding process, some organic materials, especially aromatic materials, are largely de-



composed. Apparently, the Si–O–Si bridges formed during the heating of the gel are mechanically destroyed in the process of triturating and form active centers with which organic materials can react [28,29]. The action of the mixtures of SiO_2 and Al_2O_3 used industrially as cracking catalysts can perhaps be understood in this way (cf. Fig. 13).

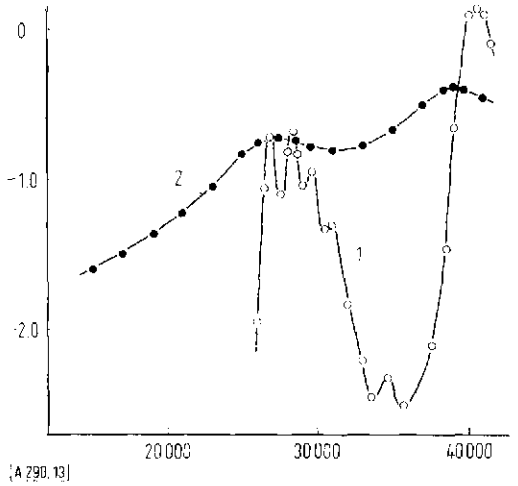


Fig. 13. Reflectance spectra of anthracene adsorbed on SiO_2 ($x = 5.0 \times 10^{-4}$). Curve 1: SiO_2 not pre-dried; Curve 2: SiO_2 dried for 1 hour at 600 °C.

Ordinate: log $F(R_\infty)$.
Abscissa: Wave number [cm^{-1}].

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German version: Angew. Chem. 75, 653 (1963).

[28] *W. A. Weyl*, Research *3*, 230 (1950).
[29] *R. E. Benson* and *J. E. Castle*, J. physic. Chem. *62*, 840 (1958).

The Biosynthesis of Alkaloids I [*]

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Dedicated to Professor Dr. Adolf Butenandt on the occasion of his 60th birthday

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   b) Hygrine, cuscohygrine, and cocaine
   c) Stachydrine
   d) Hyoscine
   e) Tropic acid
   f) Participation of C_1-metabolism
   g) Site of biosynthesis in plants
3. Pyridine and piperidine alkaloids
   a) The pyrrolidine ring of nicotine
   b) The piperidine ring of anabasine
   c) The pyridine ring of nicotine and anabasine
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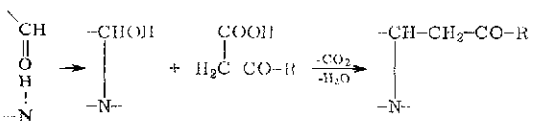
1. Introduction

The rapid development of present concepts concerning the mechanisms of biosynthesis of secondary substances in plants will soon cause a large number of classical hypotheses, no matter how ingenious some of these undoubtedly are, to pass into oblivion, because the accumulating number of experimental facts permit definite conclusions to be drawn. These in turn may lead on the one hand to entirely new theories concerning the mode of action of organisms, and on the other they may inosculate and confirm existing ideas established long before the development of modern biochemistry.

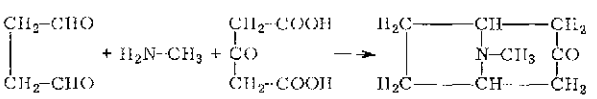
[*] Part II of this review will appear in a subsequent issue of this journal.

In the field of alkaloids, it was mainly *Trier* [1] who, in 1912, attempted to describe the synthesis of complex nitrogenous bases as part of the general metabolism of amino acids, and who stressed the existence of relationships between true (*N*-heterocyclic) alkaloids, simple plant bases, and *N*-methyl compounds of the betaine type on the one hand, and choline and amino acids on the other. *Trier*'s theoretical concepts were not restricted to special cases but were intended as the foundation of a kind of "general theory" of alkaloid formation, which was not considered exceptional but merely as a variant of already known metabolic processes. Thus, *Trier*'s theory had a high order of scientific importance. Even at that time, *Pictet* [2] carried out chemical reactions *in vitro* which supported *Trier*'s ideas. Further support came subsequently from the work of *Schöpf* [3] in particular, who carried out syntheses with possible physiological materials under "physiological" conditions, *i.e.* at room temperature and within a narrow pH-range at about pH 7. In this way, he extended the ideas of *Robinson*, whose publications in 1917 [4a-c] represent a milestone in the attempts of chemists to penetrate into the processes of nature. On the basis of *Schöpf*'s findings, the following can be considered to be the most important synthetic reactions *in vitro* [5a, b]:

1. The formation of aldehyde-ammonias from the carbonyl double bond of an aldehyde or from a CH=N double bond and the hydrogen of primary or secondary amino groups, followed by condensation of the resulting carbinolamine with the active methylene groups of ketones or β-keto acids:

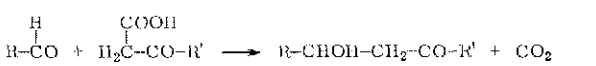


An example of this reaction is the synthesis of tropinone *(1)* from succindialdehyde *(2)*, methylamine, and acetonedicarboxylic acid on standing at room temperature for three days at pH values between 3 and 11 [6].

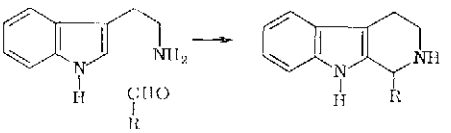


(2) *(1)*

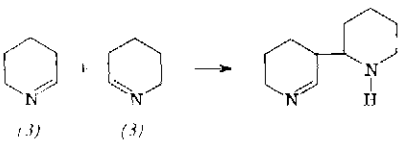
2. Aldol condensations between aldehydes and β-keto acids:



3. Condensations of β-substituted ethylamines with aldehydes; this reaction is particularly important for the synthesis of *N*-heterocyclic ring systems, *e.g.*:



4. "Aldol" condensations between CH–N double bonds and the reactive methylene group of Δ^1-piperideine *(3)*:



(3) *(3)*

These "physiological-type" [*] *in vitro* syntheses enriched organic chemistry and gave strong stimuli to biochemistry. However, it still remained unclear whether they actually represented true biosynthetic pathways in plants [3]. One objection was the optical activity usually found in naturally occurring alkaloids but absent as a matter of course in the *in vitro* syntheses. It may be assumed that spontaneous reactions, even if of any biosynthetic significance whatever, are necessarily coupled with enzymatic reactions [3].

A striking example to illustrate just how little concrete information was available as recently as a few years ago is given by the remark made by *Jucker* in 1955, who pointed out how little is really known of the pathways used by plant cells to synthetize alkaloids [7].

Recent experimental and analytical techniques have, however, brought rapid progress. Thus, in the field of basic metabolic products, the use of artificial mutants (*Neurospora* fungi, *Escherichia coli* bacteria, *etc.*) led the way to the elucidation of entire pathways in the synthesis and metabolism of the important amino acids. Thus, the existence of extremely close relationships between basic amino acids (*e.g.* ornithine, lysine), that had been emphasized so strongly by *Trier*, and heterocyclic amino acids (proline, pipecolinic acid) was demonstrated. This led to important information concerning the synthesis of true alkaloids. Moreover the coining of the term "amino acid family" made it clear how different natural substances are related to one another, *e.g.* by partially reversible reactions (*e.g.* the glutamic acid family consists of glutamic acid, α-ketoglutaric acid, ornithine, putrescine, proline, and γ-aminobutyric acid) and that it is possible to arrive at the same heterocyclic ring by similar, but not completely identical pathways, starting from different, but related substances. This gave rise to an important problem, *viz.* whether all of the preceding glutamic acid derivatives can always act as precursors for biosyntheses of the pyrrolidine system (in nicotine, tropan, *etc.*).

[1] *G. Trier:* Über einfache Pflanzenbasen und ihre Beziehungen zum Aufbau der Eiweißstoffe und Lecithine. Verlag Gebr. Borntträger, Berlin 1912, p. 117.

[2] *A. Pictet*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *244*, 389 (1906).

[3] *Cl. Schöpf*, Angew. Chem. *50*, 779, 797 (1937).

[4a] *R. Robinson*, J. chem. Soc. (London) *111*, 762 (1917).

[4b] *R. Robinson*, J. chem. Soc. (London) *111*, 876 (1917).

[4c] *R. Robinson:* The Structural Relations of Natural Products. Clarendon Press, Oxford 1955.

[5a] *Cl. Schöpf*, Angew. Chem. *61*, 31 (1949).

[5b] *H. B. Schröter* in *W. Ruhland:* Encyclopedia of Plant Physiology. Verlag Springer, Berlin 1958, Vol. 8, p. 864.

[6] *Cl. Schöpf* and *G. Lehmann*, Liebigs Ann. Chem. *518*, 1 (1935).

[*] Editor's note: The term "physiological-type" has been adopted from a paper by *E. E. van Tamelen* [Progr. Chem. org. natural Products *19*, 245 (1961)]. He defines "biogenetic-type" syntheses and "physiological-type" syntheses and states "that "biogenetic-type" syntheses are to be distinguished from "physiological-type" syntheses, in which not only plausible bioorganic substitutes are employed, but also specific conditions of temperature, pH, dilution, etc. which supposedly compare to those obtaining in a living cell."

[7] *E. Jucker*, Chimia 9, 195 (1955).

These genetic methods were introduced into biochemistry at the same time as isotopically labelled precursors, which were administered to higher plants in various ways (through the roots, by absorption through wounds in the stem, spraying onto the leaves, *etc.*). Isotopes have proved particularly important in clarifying the mutual relationships among the various alkaloids found in any given plant at the same time (in the form of primary and secondary alkaloids).

The question of the site and time of biosynthesis is also of great significance in the investigation of the mode of synthesis, since it is known that alkaloids, like many other natural substances, are formed only in definite organs [8a-d] and at certain phases of development. Thus, for example, stunted shoots of *Nicotiana glauca* can form nicotine *(31)*, nornicotine *(32)*, and anabasine *(33)* from putrescine *(24)*, but vigorously growing shoots of *N. glauca* apparently cannot do this [8d]. Owing to problems of permeability, administered precursors may not always arrive at the site of synthesis. Hence, negative results must alway be considered with caution.

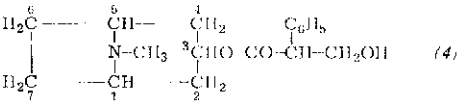
By means of these new experimental techniques, it was possible to establish the biogenetic relationships between certain "precursors" and the alkaloids within relative short periods [9a,b]. However, the finding of such relationships does not prove unequivocally whether the administered precursor is a true natural precursor or only a possible one. Usually, however, the synthetic precursor will be closely related to the natural one.

On the whole, only formal relationships have been elucidated so far. Establishment of the actual reaction mechanisms is likely to be more formidable. Fractionated homogenates and enzyme preparations will certainly be of help in this respect. The following examples will not only confirm the unusually rapid progress in our knowledge but will also demonstrate that the potential precursors discovered so far embrace only a small number of compounds or their precursors (mostly ornithine, lysine, phenylalanine, tryptophan, nicotinic acid, anthranilic acid, acetate, and mevalonic acid).

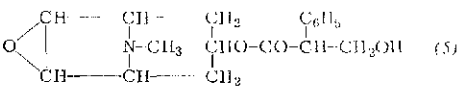
2. Tropan Alkaloids [10] and Related Compounds

The most important alkaloids of this group are hyoscyamine *(4)*, hyoscine *(5)*, and cocaine *(6)*.

Robinson's synthesis of tropinone [4a] from succindialdehyde, methylamine, and acetonedicarboxylic acid served as the starting point for his general theory that alkaloids are derived from the products of amino acid metabolism [4b, 4c]. As mentioned above, *Schöpf* synthetized tropinone under physiological conditions in 1935 [6].



(4)



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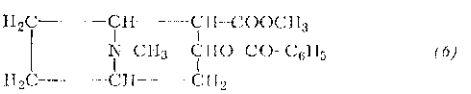
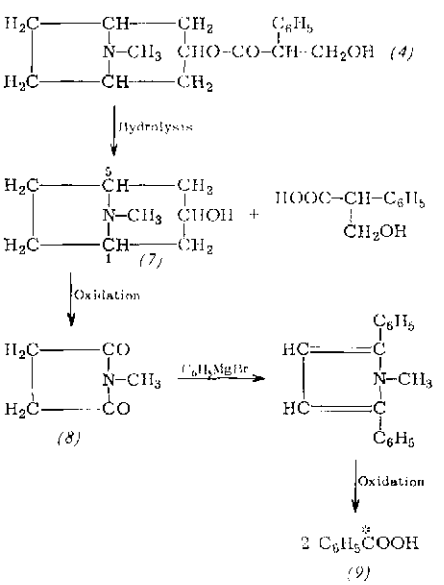


(6)

The first experiments on the mode of formation of tropan alkaloids in living plants were carried out by *James* [11] and by *Cromwell* [12], who both observed increases in the alkaloid content of isolated *Atropa* leaves after administration of arginine and ornithine or of complete *Atropa* and *Datura* plants following injections of arginine and putrescine.

a) Hyoscyamine

Incorporation of putrescine could not be confirmed in experiments with radioactively labelled compounds [13]. On the other hand, by using [2-^{14}C]ornithine, it was shown that ornithine is a biosynthetic precursor of hyoscyamine in *Datura stramonium* [14]. This would imply that the incorporation of ornithine does not proceed via the corresponding diamine putrescine. When the hyoscyamine *(4)* was isolated and degraded, all of the radioactivity was recovered in the tropine skeleton *(7)*, where, in turn, only carbon atoms C-1 and C-5 of the pyrrolidine portion were radioactive. In the degradation process used (Scheme 1), the C-1 and C-5 atoms of the



Scheme 1. Degradation of hyoscyamine *(4)*.

[8a] *K. Mothes*, Angew. Chem. *64*, 254 (1952).

[8b] *K. Mothes* and *A. Romeike* in *W. Ruhland:* Encyclopedia of Plant Physiology. Verlag Springer, Berlin 1958, Vol. 8, p. 989.

[8c] *K. Mothes*, J. Pharmacy Pharmacol. *11*, 193 (1959).

[8d] *K. Mothes* and *H. B. Schröter*, Arch. Pharmaz., Ber. dtsch. pharmaz. Ges. *294*, 99 (1961).

[9a] *K. Mothes*, Pharmazie *14*, 121, 177 (1959).

[9b] *A. R. Battersby*, Quart. Rev. (chem. Soc., London) *15*, 259 (1961).

[10] *A. Romeike*, Pharmazie *15*, 655 (1960).

[11] *W. O. James*, Nature (London) *158*, 654 (1946); New Phytologist *48*, 172 (1949).

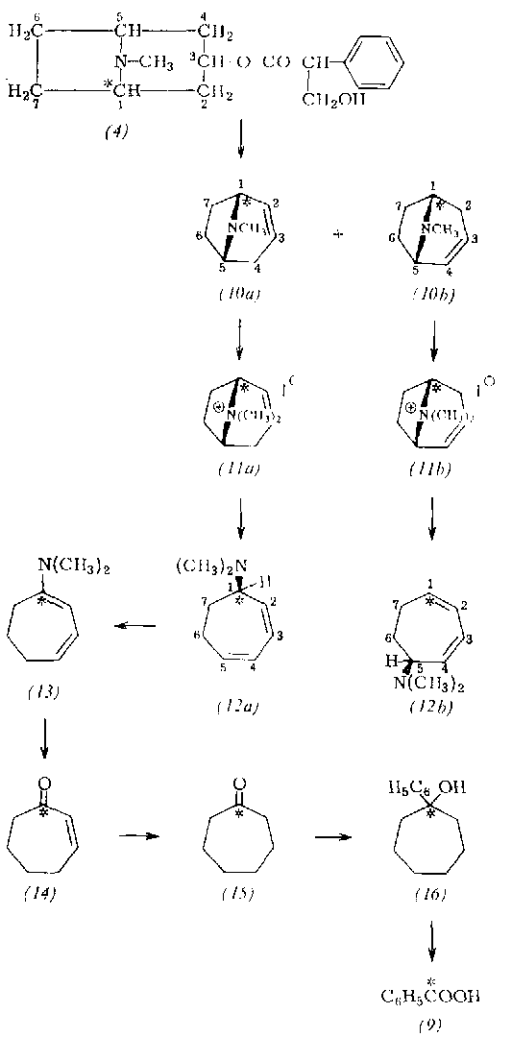
[12] *B. T. Cromwell*, Biochem. J. *37*, 722 (1944).

[13] *D. G. M. Diaper, S. Kirkwood*, and *L. Marion*, Canad. J. Chem. *29*, 964 (1951).

[14] *E. Leete, L. Marion*, and *I. D. Spenser*, Canad. J. Chem. *32*, 1116 (1954); Nature (London) *174*, 650 (1954).

tropine nucleus are equivalent, so that it cannot be decided whether the ornithine incorporation is specific, causing only one of the two carbon atoms to become labelled, or whether the incorporation proceeds via a symmetrical intermediate such as putrescine, in which the radioactivity becomes equally distributed between carbon atoms 1 and 5.

A decision in favor of the stereospecific, unsymmetrical incorporation of ornithine became possible only recently following experiments by *Dawson* et al. [15] and by *Leete* [16]. *Leete*, for example, subjected the hyoscyamine *(4)* he obtained from three-months-old *Datura stramonium* plants to pyrolysis. [2-^{14}C]Ornithine, which for clarity of discussion will be considered to be radioactive at C-1, asterisk in Scheme 2, had been aministered to the plants. The pyrolysis resulted in two isomeric tropidines *(10a)* and *(10b)*, which were transformed into their methiodides *(11a)* and *(11b)* without separation. Hofmann-degradation yielded the enantiomorphic α-methyltropidines *(12a)* and *(12b)*, which were separated with dibenzoyl-D-tartaric acid. In accordance with known

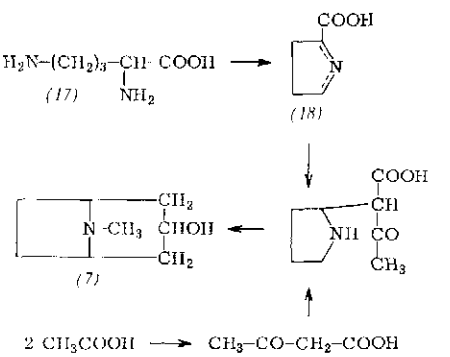


Scheme 2. Degradation of hyoscyamine *(4)* via the tropidines *(10a)* and *(10b)*.

reactions [17], heating of *(12a)* to 160 °C results in β-methyltropidine *(13)*, which is hydrolysed by dilute sulfuric acid to 2-cycloheptenone *(14)*. The carbonyl group of the latter compound corresponds to the original atom C-1; it is split off as benzoic acid *(9)* after hydrogenation to *(15)*, reaction with phenyl-lithium to give *(16)*, and oxidation. The benzoic acid had the same specific activity as the hyoscyamine initially degraded. It can therefore be concluded that only one of the two carbon atoms (1 and 5) of the hyoscyamine was radioactive and that ornithine was incorporated stereospecifically [*].

The origin of carbon atoms 2, 3, and 4 of hyoscyamine *(4)* still remained unclear. Only small amounts of radioactively labelled citric acid were incorporated into hyoscyamine by *Datura stramonium* [18].

Kaczkowski, *Schütte*, and *Mothes* [19] administered acetate labelled with ^{14}C in the methyl or carboxyl groups to cultures of isolated roots of *Datura metel* and found that up to 70–80 % was incorporated in the tropine fraction. After oxidative degradation to *N*-methylsuccinimide *(8)*, the latter, which corresponds to the pyrrolidine part, contained only 15–20 % of the activity, so that the remaining 80–85 % must be assumed to be in carbon atoms 2, 3, and 4. Further degradation studies [20], in which the carbon atom 3 was isolated as the carboxyl group of benzoic acid, showed that after administration of [1-^{14}C]acetate, carbon atom 2 contained almost all of the radioactivity, whereas it was practically inactive after administration of [2-^{14}C]acetate. These results suggest specific incorporation of the acetate into carbon atoms 2, 3, and 4. Conceivably, the synthesis of tropine proceeds via addition of acetoacetate onto a pyrrolidine derivative *(18)* from ornithine *(17)*, followed by oxidative ring-closure, reduction, and methylation to give *(7)*.



[17] *G. Merling*, Ber. dtsch. chem. Ges. *24*, 3108 (1891).

[*] Note added in proof: Recent investigations with [1,4-^{14}C$_2$]-putrescine have shown that this base can also serve as a precursor of hyoscyamine and hyoscine in isolated roots of *Datura metel*. By degradation it was demonstrated that the radioactivity of the pyrrolidine part of hyoscyamine is located exclusively in the carbon atoms adjacent to the nitrogen atom. (*H. W. Liebisch*, *H. R. Schütte*, and *K. Mothes*, unpublished results.)

[15] *A. A. Bothner-By*, *R. S. Schutz*, *R. F. Dawson*, and *M. L. Solt*, J. Amer. chem. Soc. *84*, 52 (1962).

[16] *E. Leete*, J. Amer. chem. Soc. *84*, 55 (1962).

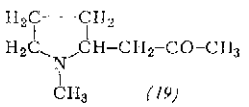
[18] *A. V. Robertson* and *L. Marion*, Canad. J. Chem. *38*, 294 (1960).

[19] *J. Kaczkowski*, *H. R. Schütte*, and *K. Mothes*, Naturwissenschaften *47*, 304 (1960).

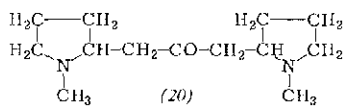
[20] *J. Kaczkowski*, *H. R. Schütte*, and *K. Mothes*, Biochim. biophysica Acta *46*, 588 (1961).

b) Hygrine, Cuscohygrine, and Cocaine

This biosynthetic pathway would also explain the formation of related alkaloids such as hygrine *(19)*, cuscohygrine *(20)*, and cocaine *(6)*.



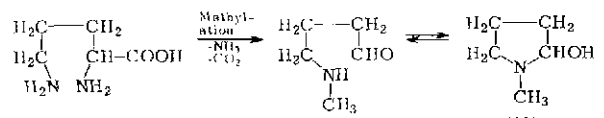
(19)



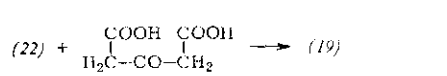
(20)

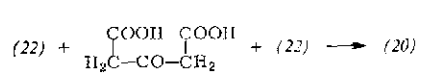
In the case of hygrine and cuscohygrine, the ring-closure leading to the formation of the tropan skeleton does not occur, while it is decarboxylation that does not occur in the formation of ecgonine, the basic component of cocaine *(6)*.

No experiments with labelled precursors have yet been carried out relative to the biosynthesis of hygrine *(19)* and cuscohygrine *(20)*. However, in confirmation of the theory of *Robinson* [4a–c], several authors [21] have been able to obtain these alkaloids in good yield under physiological conditions from γ-methylaminobutyraldehyde *(21)*, which in turn can be obtained physiologically from ornithine *(17)*, or by treating its isomeric carbinolamine *(22)* with acetoacetic acid and acetonedicarboxylic acid.

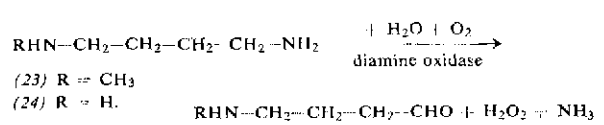


(17) *(21)* *(22)*





Hygrine *(19)* [22], cuscohygrine *(2)* [22], and norhygrine [23] have also been synthetized semi-enzymatically. Thus, in the presence of diamine oxidase, which transforms diamines into the corresponding amino aldehydes via oxidative deamination, the alkaloid hygrine *(19)* is formed in a solution of *N*-methylputrescine *(23)* and acetoacetic acid buffered at pH 7.6.



(23) R = CH_3
(24) R = H.

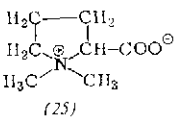
If acetonedicarboxylic acid is used instead of acetoacetic acid, hygrine *(19)* and cuscohygrine *(20)* are formed. Norhygrine is formed from putrescine *(24)* in the presence of acetoacetic acid under the above conditions.

These reactions give rise enzymatically to either γ-methylaminobutryaldehyde *(21)* or γ-aminobutyraldehyde which cyclizes spontaneously to *(22)* and reacts with the β-keto compounds according to the above scheme [either *(22)* → *(19)* or *(22)* → *(20)*]. Even if the fundamental steps of these reactions were to be achieved biosynthetically, the problem remains whether methylation takes place before ring-closure or after formation of the heterocyclic system.

No tracer experiments have yet been published on the biosynthesis of ecgonine, the basic portion of cocaine *(6)*. However, like tropinone [6], the corresponding ketone has been obtained under physiological conditions by reaction of the monomethyl ester of acetonedicarboxylic acid with methylamine and succindialdehyde at pH 5. From the fact that, in the synthesis of tropinone, the tropinone is formed directly from acetonedicarboxylic acid, succindialdehyde, and methylamine by spontaneous decarboxylation, *Schöpf* [6] concluded that, in the case of ecgonine, the esterification with methanol takes place before formation of the tropane skeleton and thereby apparently protects the carboxyl group from decarboxylation.

c) Stachydrine

Stachydrine *(25)* is the betaine of proline and can be expected to arise from ornithine just like other pyrrolidine alkaloids.



(25)

However, neither [2-^{14}C]ornithine [24], [^{14}C]proline [25], nor [2-^{14}C]glutamic acid [26] were incorporated into stachydrine by 2–3-weeks-old alfalfa plants, even though [*Me*-^{14}C]methionine [25] and [*carboxy*-^{14}C]-hygrinic acid [27] both yielded radioactive stachydrine. The authors assumed that, for reasons of permeability, only certain amino acids (*e.g.* methionine) but not others (*e.g.* neither ornithine nor proline) reached the site of stachydrine synthesis. Later experiments [28] with $^{14}CO_2$ showed, however, that *Medicago sativa* plants synthetized no stachydrine at all at the age of 2–3 weeks. Marked alkaloid synthesis could not be observed until the age of $5^1/_2$–6 months, shortly before blooming; at this stage [*carboxy*-^{14}C]proline and [2-^{14}C]ornithine were specifically incorporated into the alkaloid, thus confirming the biosynthesis of stachydrine from ornithine via proline and hygrinic acid. The initial failures show clearly how important it is to carry out physiological experiments before conducting actual biosynthetic studies.

d) Hyoscine

Incorporation experiments of *Leete* et al. [14] using [2-^{14}C]ornithine and four-months-old *Datura stramo-*

[21] *E. Anet, G. K. Hughes*, and *F. Ritchie*, Nature (London) *163*, 289 (1949); *164*, 501 (1949); *F. Galinovsky, A. Wagner*, and *R. Weiser*, Mh. Chem. *82*, 551 (1951).

[22] *H. Tuppy* and *M. S. Faltaous*, Mh. Chem. *91*, 167 (1960).

[23] *A. T. Clarke* and *P. J. G. Mann*, Biochem. J. *71*, 596 (1959).

[24] *E. Leete, L. Marion*, and *I. D. Spenser*, J. biol. Chemistry *214*, 71 (1955); *A. Morgan* and *L. Marion*, Canad. J. Chem. *34*, 1704 (1956).

[25] *A. V. Robertson* and *L. Marion*, Canad. J. Chem. *37*, 1197 (1959).

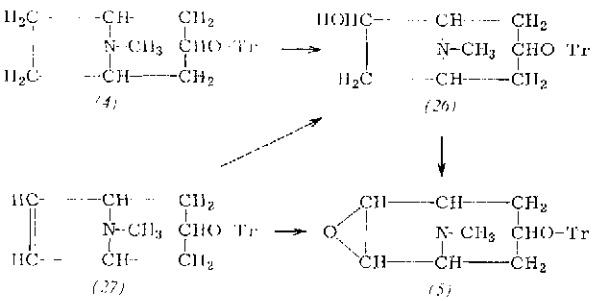
[26] *G. Wiehler* and *L. Marion*, J. biol. Chemistry *231*, 799 (1958).

[27] *A. V. Robertson* and *L. Marion*, Canad. J. Chem. *38*, 396 (1960).

[28] *J. M. Essery, D. J. McCaldin*, and *L. Marion*, Phytochemistry *1*, 209 (1962).

nium plants yielded radioactive hyoscyamine *(4)*, but the isolated hyoscine *(5)* was not radioactive. The possibility that each of the alkaloids [29] had a different biosynthetic pathway was contradicted by other work. The finding that, in various plants containing hyoscine, the fraction of the total alkaloid content represented by hyoscine is largest in younger plants [30] suggested that the *Datura stramonium* plants used by *Leete* were too old and were no longer able to synthetize hyoscine; this fact was later confirmed [31] and represents an excellent example of why negative results must be interpreted with caution.

It was later not only shown that scopolamine *(5)* and hyoscyamine *(4)* are synthetized by the same pathway, but also that the former is derived from the latter [32] by catalysis with a highly substrate-specific enzyme

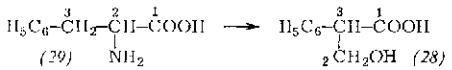


system [33]. 6-Hydroxyhyoscyamine *(26)*, which occurs as a secondary alkaloid, is an intermediate in this reaction [34].

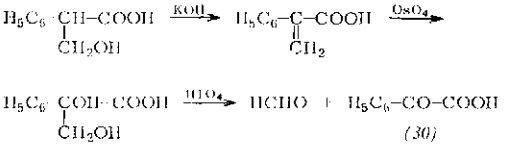
6-Dehydrohyoscyamine *(27)* is also transformed into hyoscine by *Datura ferox* [33], presumably via 6-hydroxyhyoscyamine *(26)*.

e) Tropic Acid

Phenylalanine *(29)* is definitely the precursor of tropic acid *(28)*.



The carbon atoms in the above formulae for phenylalanine and tropic acid are numbered so as to indicate the way in which they correspond biosynthetically. [3-^{14}C]Phenylalanine thus yields tropic acid in which the radioactivity is localized in carbon atom 3 [35–37], as was shown by oxidation to benzoic acid. After administration of [2-^{14}C]phenylalanine, the radioactivity was incorporated into the hydroxymethyl group of *(28)* (carbon atom 2) [38]. This carbon atom was split off as formaldehyde:



After application of [1-^{14}C]phenylalanine and execution of the same degradation scheme and subsequent decarboxylation of the phenylglyoxylic acid *(30)* obtained, the carboxyl group of tropic acid *(28)* was shown [39] to be derived from the corresponding group of phenylalanine. This is confirmed by the fact that, after administration of [1-^{14}C]phenylacetic acid, which corresponds to [2-^{14}C]phenylalanine, the carboxyl group of the tropic acid was not labelled [36]. On the basis of these experiments, it must be assumed that the phenylalanine side-chain undergoes a new type of intramolecular rearrangement in the biosynthesis of tropic acid. The incorporation of the radioactivity of [3-^{14}C]tryptophan into the carboxyl group of tropic acid [40] is difficult to understand.

In cocaine *(6)*, ecgonine is esterified with benzoic acid. Experiments with *Erythroxylon novogranatense* have shown that [3-^{14}C] phenylalanine becomes incorporated into cocaine, the radioactivity being localized almost exclusively in the benzoyl group [37]. This indicates that phenylalanine must also be looked upon as a precursor of benzoic acid.

f) Participation of C_1-Metabolism

Radioactively labelled compounds which play a role in C_1-metabolism such as [*Me*-^{14}C]methionine, sodium [^{14}C]formate [35, 36], and [^{14}C]formaldehyde [35] contribute exclusively to the radioactivity of the tropan portion of hyoscyamine and scopolamine. After administration of [*Me*-^{14}C]methionine, almost all of the radioactivity was found in the *N*-methyl group [31, 35]; this indicates that transmethylation had taken place. [^{14}C]Methylamine is not incorporated into tropan alkaloids by *Atropa belladonna* [41].

g) Site of Biosynthesis in Plants

In most of the solanaceous plants investigated, the tropan alkaloids, like nicotine, are primarily products of root

[29] *P. Reinouts van Haga*, Biochim. biophysica Acta *19*, 562 (1956).

[30] *W. C. Evans* and *M. W. Partridge*, J. Pharmacy Pharmacol. *5*, 772 (1953); *R. Hegnauer*, Pharmac. Weekbl. *86*, 321, 805 (1951); *A. Romeike*, Pharmazie *8*, 668, 729 (1953); *E. M. Trautner*, Austral. chem. Inst. J. Proc. *14*, 411 (1947).

[31] *L. Marion* and *A. F. Thomas*, Canad. J. Chem. *33*, 1853 (1955); *E. Leete*, J. Amer. chem. Soc. *82*, 612 (1960).

[32] *K. Mothes* and *A. Romeike*, Naturwissenschaften *42*, 631 (1955); *A. Romeike*, Flora *143*, 67 (1956); *A. Romeike* and *G. Fodor*, Tetrahedron Letters *1960*, No. 22, p. 1.

[33] *G. Fodor*, *A. Romeike*, *G. Janzso*, and *I. Koczor*, Tetrahedron Letters *1959*, No. 7, p. 19.

[34] *A. Romeike*, Naturwissenschaften *47*, 64 (1960); *49*, 281 (1962); *G. Fodor*, Chem. and Ind. *1961*, 1500.

[35] *E. Leete*, J. Amer. chem. Soc. *82*, 612 (1960).

[36] *E. W. Underhill* and *H. W. Youngken*, J. Pharmac. Sci. *51*, 121 (1962).

[37] *D. Gross* and *H. R. Schütte*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *296*, 1 (1963).

[38] *E. Leete* and *M. L. Louden*, Chem. and Ind. *1961*, 1405.

[39] *M. L. Louden* and *E. Leete*, J. Amer. chem. Soc. *84*, 1510 (1962); J. Amer. chem. Soc. *84*, 4507 (1962)

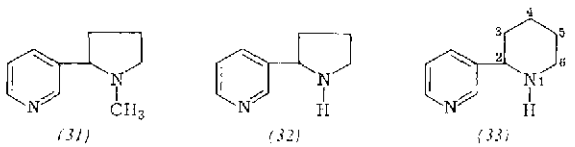
[40] *A. M. Goodeve* and *E. Ramstad*, Experientia *17*, 124 (1961).

[41] *J. R. Catch* and *E. A. Evans*, Nature (London) *188*, 758 (1960).

metabolism, although small amounts may also be formed in young shoots and in the developing fruit [42]. As was shown by the detection of an atropine esterase in juice pressed from the roots of *Datura stramonium*, the esterification of the tropan portion and tropic acid occurs primarily in the root [43]. This enzyme catalyzes both the hydrolysis of hyoscyamine and its synthesis from tropine and tropic acid. Scopine, the basic component of scopolamine, and tropic acid are also esterified in the roots of *Datura ferox*; the surface organs of the plant appear incapable of carrying out this function [44]. In the reaction hyoscyamine → scopolamine, which involves epoxide formation, the situation is reversed; this transformation takes place primarily in the surface organs [31], while the roots are either unable to synthetize scopolamine from hyoscyamine or can do this only in certain species [44, 45].

3. Pyridine and Piperidine Alkaloids

Nicotine [31] is the alkaloid of this group that has been studied most. It occurs not only in varieties of tobacco but also in other plant families [46]. Its wide distribution



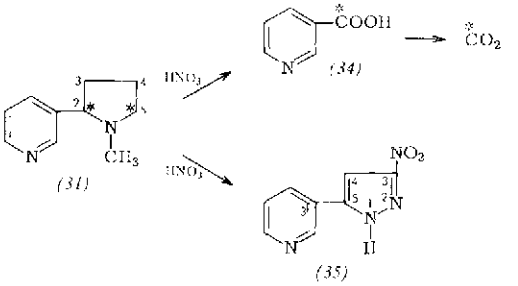
(31) *(32)* *(33)*

indicates that it can be synthetized relatively easily from ubiquitous precursors. The secondary alkaloids nornicotine *(32)* and anabasine *(33)* are related to nicotine.

A number of hypotheses have been proposed concerning the biosynthesis of nicotine and anabasine, the most noteworthy being those which postulate [4c] that nicotinic acid or lysine are the precursors of the pyridine ring and that ornithine is the precursor of the pyrrolidine ring in nicotine. Lysine is suggested as the precursor of the piperidine ring in anabasine [4c].

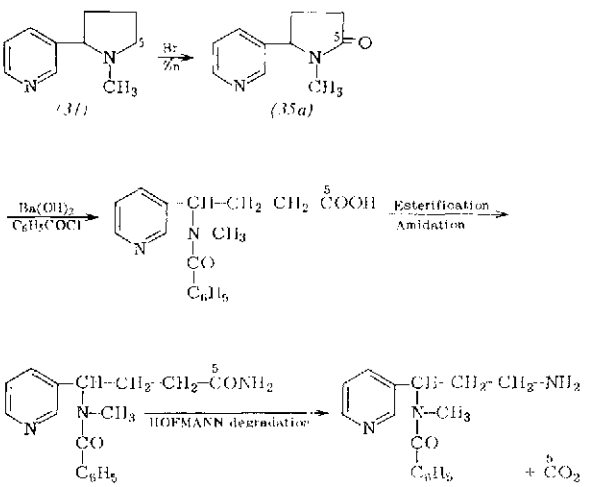
a) The Pyrrolidine Ring of Nicotine

Radioactive nicotine *(31)* was obtained after administration of [2-^{14}C]ornithine *(17)* to *Nicotiana rustica* [47a, b] or *N. tabacum* [48]. Degradation of the labelled alkaloid to nicotinic acid *(34)* and CO_2 (from the carbonyl group of nicotinic acid) showed that half of the radioactivity was in carbon atom 2 of the pyrrolidine ring; this indicates a distribution of activity corresponding to the asterisks in formula *(31)*. This was proved by a study of a secondary product obtained by oxidation of nicotine with nitric acid, *viz.* 3-nitro-5-(pyrid-3′-yl)pyrazole *(35)*



(31) *(34)* *(35)*

[49]. This compound includes all the carbon atoms of the original nicotine with the exception of C-5 and the carbon atom of the *N*-methyl group. This pyrazole derivative contains half of the specific activity of the nicotine [50]. Since the *N*-methyl group of the alkaloid was inactive, the remaining radioactivity must have been in carbon atom 5 of the pyrrolidine ring, which was isolated as CO_2 by degradation via cotinine *(35a)* [47b].



(31) *(35a)*

The occurrence of radioactivity in carbon atoms 2 and 5 of the pyrrolidine ring after administration of [2-^{14}C]-ornithine indicates the formation of a symmetrical intermediate in the synthesis of this portion of nicotine.

Although their degrees of incorporation are lower than that of ornithine, [1,4-$^{14}C_2$]putrescine *(24)* [51], uniformly labelled [^{14}C]proline [51], and [2-^{14}C]glutamic acid *(36)* [51,52] also serve as precursors for the pyrrolidine ring of nicotine. The lower degrees of incorporation may be due to permeability factors or the high concentration of free glutamic acid in tobacco [53]. The specific degree of incorporation into the pyrrolidine ring has been determined for all of these com-

[42] *K. Mothes* and *A. Romeike* in *W. Ruhland:* Encyclopedia of Plant Physiology. Springer, Berlin 1958, Vol. 8, p. 1008; *A. Romeike*, Pharmazie *8*, 668, 729 (1953); *Sh. Shibata*, Planta med. *4*, 74 (1956).

[43] *A. Jindra, S. Zadrazil*, and *S. Cerna*, Collect. czechoslov. chem. Commun. *24*, 2761 (1959); *J. Andrzejczuk* and *J. Kaczkowski*, Acta Soc. botan. polon. *31*, 461 (1962); *A. Jindra, S. Leblova, Z. Sipal*, and *A. Cihak*, Planta med. *8*, 44 (1960).

[44] *A. Romeike*, Flora *148*, 306 (1959).

[45] *A. Romeike*, Naturwissenschaften *46*, 492 (1959); Planta medica *8*, 491 (1960).

[46] *K. Mothes*, J. Pharmacy Pharmacol. *11*, 193 (1959).

[47a] *L. J. Dewey, R. U. Byerrum*, and *C. D. Ball*, Biochim. biophysica Acta *18*, 141 (1955).

[47b] *B. L. Lamberts, L. J. Dewey*, and *R. U. Byerrum*, Biochim. biophysica Acta *33*, 22 (1959).

[48] *E. Leete*, Chem. and Ind. *1955*, 537.

[49] *G. R. Clemo* and *T. Holmes*, J. chem. Soc. (London) *1934*, 1739.

[50] *E. Leete* and *K. Siegfried*, J. Amer. chem. Soc. *79*, 4529 (1957).

[51] *E. Leete*, J. Amer. chem. Soc. *80*, 2162 (1958).

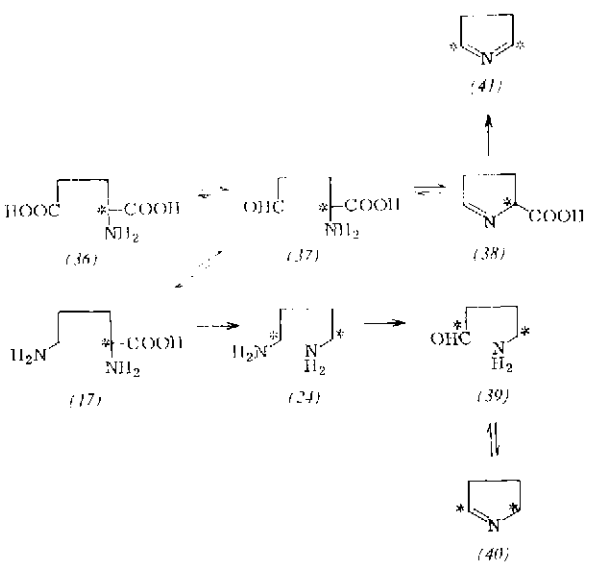
[51a] *K. Hasse* and *P. Homann*, Biochem. Z. *335*, 474 (1962); *K. Hasse* and *K. Schührer*, ibid. *336*, 20 (1962).

[52] *B. L. Lamberts* and *R. U. Byerrum*, J. biol. Chemistry *233*, 939 (1958).

[53] *B. Commoner* and *N. Varda*, J. gen. Physiol. *36*, 791 (1953); *E. A. H. Roberts* and *D. N. Wood*, Arch. Biochem. Biophysics *33*, 299 (1951).

pounds; the radioactivity of both [1,4-$^{14}C_2$]putrescine and [2-^{14}C]glutamic acid was equally distributed between carbon atoms 2 and 5 of the pyrrolidine ring.

In animal systems and in microorganisms, glutamic acid, proline, and ornithine are closely related [54] via α-amino-γ-formylbutyric acid *(37)* and Δ^1-pyrroline-5-carboxylic acid *(38)*. On the other hand, a widely distributed diamine oxidase can oxidize putrescine *(24)* to γ-aminobutyraldehyde *(39)*, which in turn cyclizes spontaneously to a Δ^1-pyrroline *(40)* [55]. On the basis of these results, *Leete* discusses a synthesis of Δ^1-pyrroline, in which putrescine or a mesomeric anion *(41)* is postulated as a symmetrical intermediate [51] (see also [51a]). Δ^1-Pyrroline would then be the direct precursor of the pyrrolidine portion of nicotine. [5-^{14}C]-Δ^1-Pyrroline-5-carboxylic acid *(38)* is in fact specifically incorporated into the pyrrolidine ring of nicotine by *Nicotiana rustica* [56]. Most of the activity occurs in carbon atoms 2 and 5. The distribution of radioactivity in the pyrrolidine ring of nicotine after administration of [1-^{14}C]acetate, [2-^{14}C]acetate, [2-^{14}C]propionate, [3-^{14}C]propionate, [1,3-$^{14}C_2$]glycerol, [2-^{14}C]glycerol, and [3-^{14}C]aspartic acid to *Nicotiana rustica* can readily be explained by assuming that all of theses compounds end up in the citric acid cycle and are incorporated into nicotine via glutamate [57].

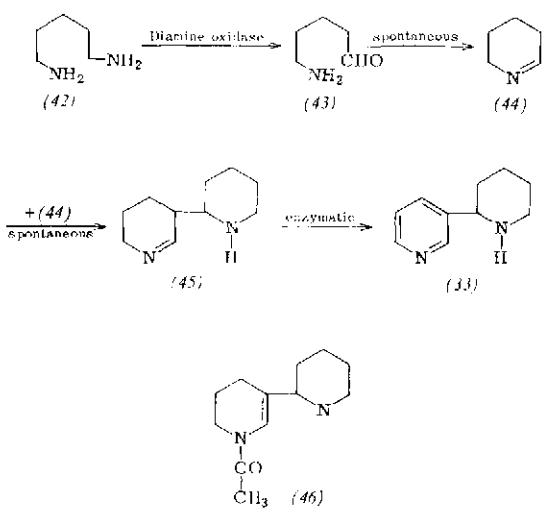


b) The Piperidine Ring of Anabasine

In anabasine *(33)*, there is a piperidine ring which corresponds to the pyrrolidine ring in nicotine. According to theory [4c] (see above), the pyridine and piperidine rings of anabasine are supposed to be derived from lysine. [2-^{14}C]Lysine [58] and [1,5-$^{14}C_2$]cadaverine *(42)* [59] are in fact incorporated into anabasine by *N. glauca*, but only into the piperidine ring. The pyridine ring, which could theoretically also be derived from lysine [4c], had no radioactivity in these experiments. The nicotine in *N. tabacum* is also non-radioactive [58] after administration of [2-^{14}C]lysine, so that lysine can be excluded as a precursor of the pyridine ring in *Nicotiana* species.

Carbon atom 2 of anabasine contains only half of the radioactivity after administration of [1,5-$^{14}C_2$]cadaverine. In analogy with the incorporation of putrescine into nicotine [59], this indicates that the radioactivity has been distributed equally between carbon atoms 2 and 6; however, after administration of [2-^{14}C]lysine, all of the radioactivity has been reported to be in carbon atom 2 (next to the pyridine ring), in contrast to the mode of incorporation of ornithine into nicotine; consequently, the mechanisms for the synthesis of nicotine and anabasine [58] are different. The latter synthesis may possibly involve a non-symmetrical lysine degradation product of the type of Δ^1-piperidine-2-carboxylic acid [51a].

Anabasine may also arise, however, by a quite different pathway. Extracts prepared from pea or lupin seedlings contain a diamine oxidase that can oxidize cadaverine *(42)* to ω-aminovaleraldehyde *(43)* [55]; this aldehyde cyclizes spontaneously to Δ^1-piperideine *(44)*, which dimerizes under suitable conditions to tetrahydroanabasine *(45)* [60]. The plant extracts mentioned above also contain a factor of low molecular weight dependent upon Mn ion that is able to oxidize tetrahydroanabasine to anabasine *(33)* [61]. This anabasine synthesis has been confirmed with [1,5-$^{14}C_2$]cadaverine [62], however, it has not proved possible to demonstrate the existence of this pathway in intact plants. Nevertheless, it is of importance, as it represents the first enzymatic synthesis of alkaloids *in vitro* and because tetrahydroanabasines of the type of ammodendrine *(46)* [63], for which [1,5-$^{14}C_2$]cadaverine can serve as a precursor in *Ammodendron conollyi* [64], occur in several Leguminosae.



[54] *M. R. Stetten* in *W. D. McElroy* and *H. B. Glass:* Amino Acid Metabolism. Johns Hopkins Press, Baltimore 1955, p. 277; *H. J. Vogel*, ibid. p. 335.

[55] *P. J. G. Mann* and *W. R. Smithies*, Biochem. J. *61*, 89 (1955); *K. Hasse* and *H. Maisack*, Naturwissenschaften *42*, 627 (1955); Biochem. Z. *327*, 296 (1955).

[56] *V. Krampl* and *C. A. Hoppert*, Federat. Proc. *20*, 375 (1961).

[57] *P. H. L. Wu*, *T. Griffith*, and *R. U. Byerrum*, J. biol. Chemistry *237*, 887 (1962).

[58] *E. Leete*, J. Amer. chem. Soc. *78*, 3520 (1956).

[59] *E. Leete*, J. Amer. chem. Soc. *80*, 4393 (1958).

[60] *Cl. Schöpf*, *F. Braun*, and *A. Komzak*, Chem. Ber. *89*, 1821 (1956).

[61] *K. Hasse* and *P. Berg*, Naturwissenschaften *44*, 584 (1957); Biochem. Z. *331*, 349 (1959).

[62] *K. Mothes*, *H. R. Schütte*, *H. Simon*, and *F. Weygand*. Z. Naturforsch. *14 b*, 49 (1959).

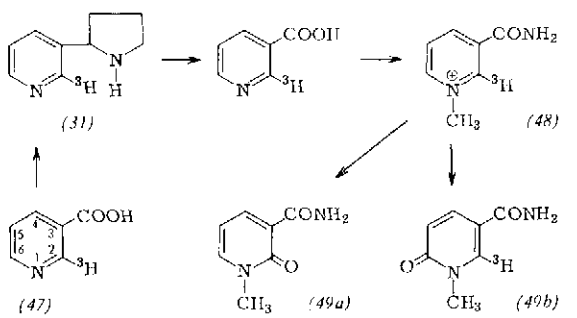
[63] *H. G. Boit:* Ergebnisse der Alkaloid-Chemie bis 1960. Akademie-Verlag, Berlin 1961.

[64] *H. R. Schütte* and *K. Mothes*, unpublished results.

c) The Pyridine Ring of Nicotine and Anabasine

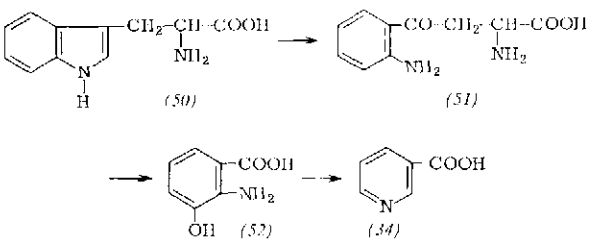
The synthesis of anabasine, where both the pyridine and pipcridine rings are formed from cadaverine, raises the question how the pyridine ring of nicotine and anabasine originates in *Nicotiana* species. *Trier* [4c, 65] had already suggested that nicotine is formed from nicotinic acid and proline. Administration of nicotinic acid does in fact seem to result in an increase in nicotine content [66]. However, [*carboxy*-^{14}C]nicotinic acid or its esters are not incorporated into nicotine [67]. [2-^{14}C]Tryptophan too is not incorporated into nicotine [68]. The pyridine ring was unlabelled following administration of [2-^{14}C]lysine [58, 69]. In experiments with sterile root cultures of *Nicotiana tabacum*, nicotinic acid labelled with radiocarhon or tritium in the aromatic ring was incorporated into the pyridine ring of nicotine [70]. The carboxyl group is apparently split off in the course of the synthesis of nicotine from nicotinic acid.

Dawson et al. [70] gained greater insight into the mechanism of this reaction by using nicotinic acid specifically labelled with tritium or deuterium. [2-^{3}H]Nicotinic acid, [4-^{2}H]nicotinic acid, and [5-^{3}H]nicotinic acid each showed comparable degrees of incorporation, similar to that for uniformely labelled [^{14}C]nicotinic acid or [^{3}H]nicotinic acid. The nicotine *(31)* obtained from [2-^{3}H]nicotinic acid *(47)* was degraded to a mixture of 2-pyridone *(49a)* and 6-pyridone *(49b)* by oxidation to nicotinic acid, which in turn was transformed to 1-methyl nicotinamide *(48)* and then oxidized with potassium ferricyanide. In contrast to the 6-pyridone *(49b)*,



the 2-pyridone *(49a)* obtained by this process was practically unlabelled; this indicates a specific mode of incorporation for nicotinic acid and the absence of a symmetrical intermediate. The results obtained after administration of [6-^{3}H]nicotinic acid were quite different; here, the authors [70] found only approximately one tenth of the degree of incorporation obtained with nicotinic acid labelled in other ways. The 6-position of the nicotinic acid is thus metabolized during the transformation of nicotinic acid to nicotine. There is still no information as to the nature of the intermediate in this reaction. A 6-pyridone and a 1,6-dihydropyridinium compound have been suggested. The first possibility is contradicted by the fact that 6-hydroxy[^{15}N]nicotinic acid is not incorporated into nicotine [70]. 6-Oxo-1-methyl-[2-^{3}H]nicotinamide is not incorporated to any significant extent either [70]. The pyridine ring of anabasine is formed in the same way as that of nicotine [71].

What is the origin of nicotinic acid? It has been shown for animals and certain microorganisms that nicotinic acid *(34)* is synthetized from tryptophan *(50)* via kynurenine *(51)* and 3-hydroxyanthranilic acid *(52)* [72].



In higher plants [73] and certain bacteria [74], however, experiments with tryptophan labelled with ^{14}C or ^{3}H have so far failed to show any transformation to nicotinic acid. Radioactive acetate, especially methyl-labelled acetate, is incorporated into nicotine by *N. tabacum* [75–78] in large quantities and into anabasine by *N. glauca* [76]. In the presence of inactive nicotinic acid, the degree of incorporation of [2-^{14}C]acetate is significantly smaller than in its absence. Inactive nicotinic acid apparently suppresses the biosynthesis of radioactive acid from labelled acetate [76].

Degradation of the anabasine obtained from the experiment with [2-^{14}C]acetate (without addition of inactive nicotinic acid) showed that approximately 95 %

[65] *E. Winterstein* and *G. Trier:* Die Alkaloide. Borntraeger, Berlin 1931, p. 1031.

[66] *G. Klein* and *H. Linser*, Planta *20*, 470 (1933); *R. F. Dawson*, Plant Physiol. *14*, 479 (1939); *R. F. Dawson*, Ann. Rev. Biochem. *17*, 541 (1948).

[67] *R. F. Dawson, D. R. Christman*, and *R. C. Anderson*, J. Amer. chem. Soc. *75*, 5114 (1953).

[68] *P. J. Mortimer*, Nature (London) *172*, 74 (1953); *U. Bowden*, ibid. *172*, 768 (1953).

[69] *A. A. Bothner-By, R. F. Dawson*, and *D. R. Christman*, Experientia *12*, 151 (1956).

[70a] *R. F. Dawson, D. R. Christman, A. F. D'Adamo, M. L. Solt*, and *A. P. Wolf*, J. Amer. chem. Soc. *82*, 2628 (1960); Chem. and Ind. *1958*, 100.

[70b] *R. F. Dawson, D. R. Christman, R. C. Anderson, M. L. Solt, A. F. D'Adamo*, and *U. Weiss*, J. Amer. chem. Soc. *78*, 2645 (1956).

[71] *M. L. Solt, R. F. Dawson*, and *D. R. Christman*, Plant Physiol. *35*, 887 (1960).

[72] *A. H. Mehler* in *W. D. McElroy*, and *H. B. Glass:* Amino Acid Metabolism. Johns Hopkins Press, Baltimore 1955, p. 882; *C. Yanofsky*, ibid. p. 930.

[73a] *E. Leete, L. Marion*, and *I. D. Spenser*, Canad. J. Chem. *33*, 405 (1955).

[73b] *S. Aronoff*, Plant Physiol. *31*, 355 (1956).

[73c] *E. Leete*, Chem. and Ind. *1957*, 1270.

[73d] *J. Grimshaw* and *L. Marion*, Nature (London) *181*, 112 (1958).

[73e] *L. M. Henderson, J. F. Someroski, D. R. Rao, P. H. L. Wu, T. Griffith*, and *R. U. Byerrum*, J. biol. Chemistry *234*, 93 (1959).

[74] *C. Yanofsky*, J. Bacteriol. *68*, 577 (1954).

[75] *G. S. Iljin*, Dokl. Akad. Nauk SSSR *119*, 544 (1958).

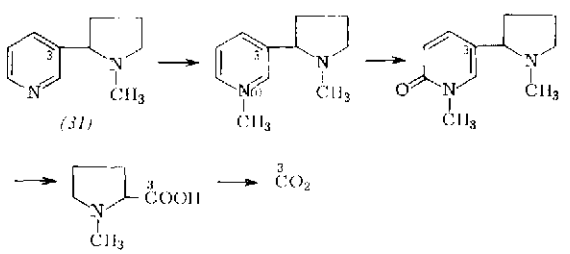
[76] *E. Leete*, Chem. and Ind. *1958*, 1477.

[76a] *E. G. Bilinski* and *W. B. McConnell*, Canad. J. Biochem. Physiol. *35*, 357 (1957).

[77] *T. Griffith* and *R. U. Byerrum*, Science (Washington) *129*, 1485 (1959); *T. Griffith* and *R. U. Byerrum*, Federat. Proc. *18*, 942 (1959).

[78] *T. Griffith, K. P. Hellmann*, and *R. U. Byerrum*, J. biol. Chemistry *235*, 800 (1960); *T. Griffith* and *R. U. Byerrum*, Federat. Proc. *18*, 942 (1959).

of the radioactivity was in the pyridine ring [76], while in the nicotine, the radioactivity was distributed between the pyridine and the pyrrolidine rings [76,77]. This difference in results between nicotine and anabasine is understandable, because the pyrrolidine ring of nicotine is more closely related to acetate via the glutamic acid/ornithine/proline family and the Krebs cycle than lysine is, and lysine is the precursor of the piperidine ring in anabasine [76a]. In seven-day experiments with *N. rustica*, [1-^{14}C]acetate was incorporated exclusively into the pyrrolidine ring of nicotine [77]. [1-^{14}C]Pyruvic acid was incorporated to a very small extent, while [3-^{14}C]pyruvic acid, which corresponds to [2-^{14}C]-acetate was incorporated rapidly [77]. Uniformly labelled [^{14}C]aspartic acid is also incorporated into the pyridine ring of nicotine, but the degree of incorporation is not much higher than that of acetate [76]. [3-^{14}C]-Aspartic acid is incorporated very rapidly into the pyridine ring; in this case, approximately half of the radioactivity is localized in carbon atom 3 of the pyridine ring, as was shown by degradation illustrated in Scheme 3 [79].



(31)

Scheme 3. Degradation of nicotine.

Whereas radioactivity from [1-^{14}C]propionate is barely incorporated at all into nicotine, [2-^{14}C]propionate and [1,3-$^{14}C_2$]glycerol show a much higher degree of incorporation than [2-^{14}C]acetate [78]. By using a specific degradation procedure, it was possible to isolate carbon atom 3 of the pyridine ring. The distribution of radioactivity in the pyrrolidine ring following administration of [2-^{14}C]propionate and [1,3-$^{14}C_2$]glycerol corresponds to that following incorporation of [2-^{14}C]acetate. [1-^{14}C]Propionate is incorporated to only a minor extent. It is known that propionate can be either carboxylated to give methylmalonate [80], which then rearranges to succinate, or is catabolized by β-oxidation and subsequent elimination of the original carboxyl group to give acetate [81]. Both reactions effectively introduce the propionate into the Krebs cycle. [1,3-$^{14}C_2$]Glycerol can also be degraded to [2-^{14}C]acetate by glycolysis, so that the similarity in distribution of the radioactivity in these three experiments is quite understandable.

It was found that 39 % of the activity of [2-^{14}C]propionate and 57 % of that of [1,3-$^{14}C_2$]glycerol recur in the pyridine ring and that half of the activity of the pyridine is located at carbon atom 3 in the experiments with both [2-^{14}C]propionate and [2-^{14}C]acetate [78,79]. Although this distribution is also to be expected on conversion of the propionate into acetate or succinate, the investigators concluded [78] from the higher degree of incorporation of [2-^{14}C]propionate into nicotine (relative to that of [2-^{14}C]acetate) and from the higher occurrence in the pyridine ring of activity from [1,3-$^{14}C_2$]glycerol (60 %) relative to that from [2-^{14}C]acetate (40 % in the pyridine ring) that the Krebs cycle is not involved here but that both of these compounds lie directly on the synthetic pathway leading to the pyridine ring [82]. The carboxyl group of propionic acid thus becomes the carboxyl group in nicotinic acid. However, this carboxyl group is lost during the course of the synthesis of nicotine; this would explain the low degree of incorporation of radiocarbon from [1-^{14}C]propionate. However, this carboxyl group would also be lost by transformation to acetate or succinic acid on passing through the Krebs cycle.

The hypothesis of direct incorporation of propionate into nicotinic acid was disproved by an experiment with [3-^{14}C]propionate. This compound does not result in activity in the pyridine ring of nicotine. It must therefore be assumed that propionate passes into the Krebs cycle via acetate, [3-^{14}C]propionate thus corresponding to [1-^{14}C]acetate [79].

The direct incorporation of glycerol into the pyridine ring of nicotine is indicated by the fact that [1,3-$^{14}C_2$]-glycerol is incorporated to the same extent as [2-^{14}C]-glycerol [79]. If glycerol were incorporated via glycolysis and the Krebs cycle, then [2-^{14}C]glycerol would yield [1-^{14}C]acetate, which according to previsous experiments is incorporated only very poorly [77]. In other experiments, [2-^{14}C]glycerol was found to be incorporated to twice the extent of [1,3-$^{14}C_2$]glycerol [83].

Further experiments will be necessary to clear up the various remaining questions. In animals, β-alanine, which can be formed from propionic and aspartic acids [84], is a precursor of quinolinic acid *(53)*, which is related to nicotinic acid [85]. In experiments with *Escherichia coli*, glycerol and succinic acid were found to be precursors of nicotinic acid [86]. Experiments with either [1,3-^{14}C]glycerol and unlabelled succinic acid or [2,3-$^{14}C_2$]succinic acid and unlabelled glycerol had shown that only the pyridine ring became labelled. However, following administration of [1,4-$^{14}C_2$]-succinic acid and inactive glycerol, the pyridine ring of nicotinic acid was unlabelled, and all of the radioactivity was found in the carboxyl group [87]. In experiments with *Mycobacterium tuberculosis* strain BCG, all of the activity was found in the carboxyl group of nicotinic acid following administration of [4-^{14}C]aspartic acid. After administration of [1,4-$^{14}C_2$,^{15}N]aspartic acid, the carboxyl group still had all the radioactivity; the ratio of $^{14}C/^{15}N$ in the nicotinic acid was approximately as expected on the assumptions that one molecule of aspartic acid, including its amino nitrogen, is incorporated into nicotinic acid and that the α-carboxyl

[79] *T. Griffith, K. P. Hellmann*, and *R. U. Byerrum*, Biochemistry *1*, 336 (1962).

[80] *M. Flavin, P. J. Ortiz*, and *S. Ochoa*, Nature (London) *176*, 823 (1955); *M. Flavin* and *S. Ochoa*, J. biol. Chemistry *229*, 965 (1957).

[81] *J. Giovanelli* and *P. K. Stumpf*, J. Amer. chem. Soc. *79*, 2652 (1957); J. biol. Chemistry *231*, 411 (1958).

[82] *T. Griffith* and *R. U. Byerrum*, Federat. Proc. *18*, 942 (1959).

[83] *R. F. Dawson* and *D. R. Christman* (1961), quoted after [79].

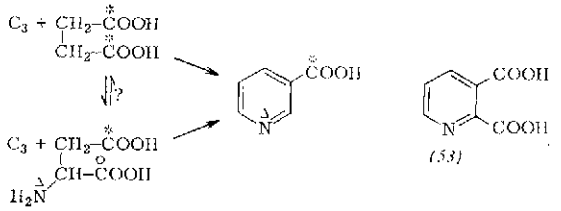
[84] *F. P. Kupiecki* and *M. J. Coon*, J. biol. Chemistry *229*, 743 (1957).

[85] *L. V. Hankes* and *M. A. Schmaeler*, Biochem. Biophysic. Res. Commun. *2*, 468 (1960).

[86] *M. V. Ortega* and *G. M. Brown*, J. Amer. chem. Soc. *81*, 4437 (1959).

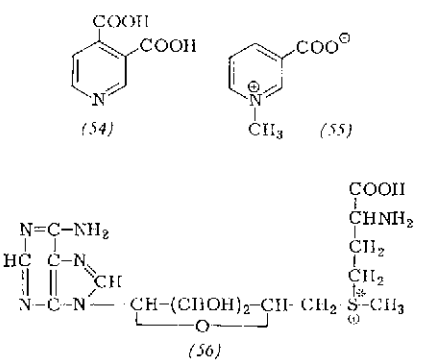
[87] *M. V. Ortega* and *G. M. Brown*, J. biol. Chemistry *235*, 2939 (1960).

group is lost [88]. The fact that in the presence of inactive succinic acid, [2-^{14}C]propionate is incorporated by *E. coli* into nicotinic acid only slightly or not all [87] indicates that propionate is not a direct precursor in these bacteria. Hence, a C_4-acid and a C_3-fragment must be assumed to be the



(53)

precursors. When nicotinic-acid-deficient mutants of *Lactobacillus arabinosus* and *E. coli* were grown in media free from nicotinic acid to which various compounds were added, they exhibited growth only with cinchomeronic acid *(54)*, [89]. The isolation of cinchomeronic acid from the filtrate from the culture medium of a nicotinic-acid-deficient mutant made it likely that this acid is the true precursor of nicotinic acid in the organism [83]. The only information available so far for trigonellin *(55)*, the betaine of nicotinic acid, is that it is not formed from ^{14}C-labelled tryptophan [73a,73e] or 3-hydroxy[7-^{14}C]anthranilic acid [73b] and that it is formed from nicotinic acid [90,91]. Extracts of pea shoots can catalyze the synthesis of trigonellin from nicotinic acid and *S*-adenosylmethionine *(56)*.



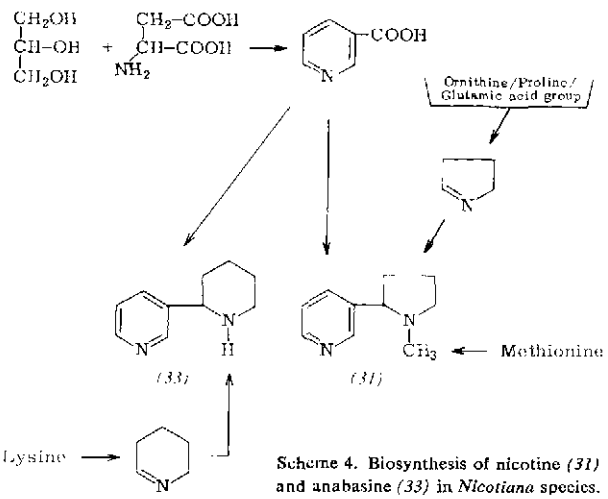
(54) (55)

(56)

d) The Methyl Group of Nicotine

The origin of the methyl group of nicotine has been intensively investigated. Several ^{14}C-labelled C_1 donors can be used, the radioactivity then being localized primarily or exclusively in the *N*-methyl group: [^{14}C]formic acid [92,93], [^{14}C]formaldehyde [94], [3-^{14}C]serine [94], [*Me*-^{14}C]methionine [92,95,96], [*Me*-^{14}C]choline [95], [*Me*-^{14}C]betaine [97], [2-^{14}C]glycolic acid [93,98], and [2-^{14}C]glycine [99]. The methylation is probably accomplished by transmethylation with active methionine *(56)* [*S*-adenosylmethionine], since when doubly labelled [*Me*-^{14}C^{2}H$_3$]methionine is used, the ^{14}C/D isotope ratio in the methyl group of nicotine is the same as that in methionine, *i.e.* the methyl group is transferred intact [96]. As expected, L-methionine is a considerably more active methyl group donor than the D-isomer [100]. It is not yet known whether primary methylation also occurs directly via the folic acid system.

This does not yet explain whether nornicotine is the precursor of nicotine, or nicotine the precursor of nornicotine, or whether both alkaloids are biosynthetized in



(33) (31)

Scheme 4. Biosynthesis of nicotine *(31)* and anabasine *(33)* in *Nicotiana* species.

parallel [9a]. Demethylation of nicotine is certainly possible [9a,101]; [*Me*-^{14}C]choline is formed after administration of [*Me*-^{14}C]nicotine to tobacco plants [102].

On the basis of the results described above, it is possible to construct a pathway (Scheme 4) for the biosynthesis of nicotine *(31)* and anabasine *(33)* in *Nicotiana* species.

e) Ricinine

Ricinine *(57)*, which is obtained from *Ricinus communis*, contains a pyridone ring. The *O*- and *N*-methyl group can be derived from methionine [103] or formate [104, 106]. Carboxyl-labelled nicotinic acid is incorporated into ricinine, the activity being localized in the cyano group [105–107].

[88] *E. Mothes, D. Gross, H. R. Schütte*, and *K. Mothes*, Naturwissenschaften *48*, 623 (1961); *D. Gross, H. R. Schütte, G. Hübner* u. *K. Mothes*, Tetrahedron Letters *1963*, in the press.

[89] *F. Lingens*, Angew. Chem. *72*, 920 (1960).

[90] *F. C. J. Zeijlemaker*, Acta bot. neerl. *2*, 123 (1953); *Cl. O. Blaka*, Amer. J. Bot. *41*, 231 (1954); *J. Brüggemann, G. Drepper*, and *U. Hadeler*, Biochem. *Z. 322*, 426 (1952).

[91] *J. G. Joshi* and *P. Handler*, J. biol. Chemistry *235*, 2981, (1960).

[92] *St. A. Brown* and *R. U. Byerrum*, J. Amer. chem. Soc. *74*, 1523 (1952).

[93] *R. U. Byerrum, L. J. Dewey, R. L. Hamill*, and *Ch. D. Ball*, J. biol. Chemistry *219*, 345 (1956).

[94] *R. U. Byerrum, R. L. Ringler, R. L. Hamill*, and *Ch. D. Ball*, J. biol. Chemistry *216*, 371 (1955).

[95] *R. U Byerrum* and *R. E. Wing*, J. biol. Chemistry *205*, 637 (1954).

[96] *L. J. Dewey, R. U. Byerrum*, and *Ch. D. Ball*, J. Amer. chem. Soc. *76*, 3997 (1954).

[97] *R. U. Byerrum, C. S. Sato*, and *Ch. D. Ball*, Plant Physiol. *31*, 374 (1956).

[98] *R. U. Byerrum, L. J. Dewey*, and *Ch. D. Ball*, Plant Physiol. *30*, XVI (1955).

[99] *R. U. Byerrum, R. L. Hamill*, and *Ch. D. Ball*, J. biol. Chemistry *210*, 645 (1954).

[100] *B. Ladesic, Z. Devide, N. Pravdic*, and *D. Keglevic*, Arch. Biochem. Biophysics *97*, 556 (1962).

[101] *K. Mothes, L. Engelbrecht, K. H. Tschöpe*, and *G. Hutschenreuter-Trefftz*, Flora *144*, 518 (1957).

[102] *E. Leete* and *V. M. Bell*, J. Amer. chem. Soc. *81*, 4358 (1959).

[103] *M. Dubeck* and *S. Kirkwood*, J. biol. Chemistry *199*, 307 (1952).

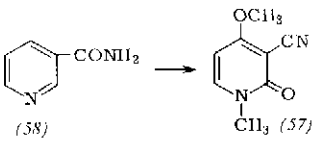
[104] *G. Boeckh-Behrens*, Ph. D. thesis, Universität Tübingen, 1960.

[105] *E. Leete* and *F. H. B. Leitz*, Chem. and Ind. *1957*, 1572.

[106] *G. R. Waller* and *L. M. Henderson*, J. biol. Chemistry *236*, 1186 (1961).

[107] *G. R. Waller* and *L. M. Henderson*, Biochem. Biophysic. Res. Commun. *5*, 5 (1961).

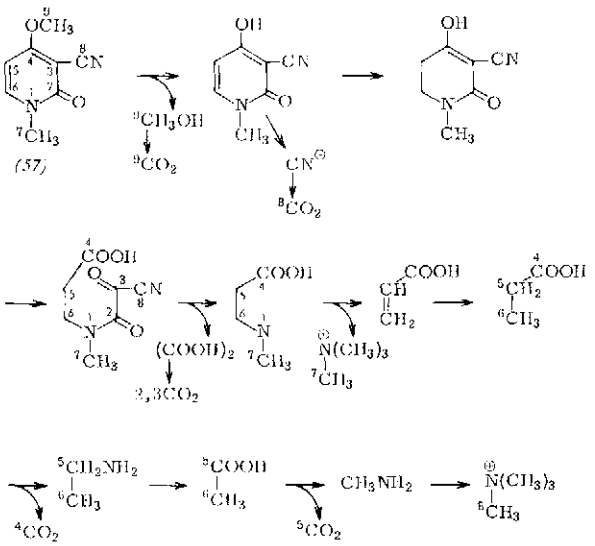
Experiments with doubly labelled nicotinic acid (^3H and $^{14}COOH$) and nicotinamide *(58)* [^3H and $^{15}NH_2$] have shown that nicotinic acid can be incorporated intact into ricinine via the amide [106]. The nitrile group is derived from the carboxamide residue. This shows that there is



(58) *(57)*

a close biogenetic relationship between this pyridone alkaloid and the pyridine derivatives such as nicotine. Moreover, the biosynthesis of ricinine is likely to provide important information also on nicotinic acid biosynthesis in higher plants.

[7a-^{14}C]Tryptophan is not incorporated into ricinine [106]. Here again, all the results indicate that the pyridine ring is formed from smaller precursors. Thus, experiments with a variety of labelled compounds [76, 104, 106–108] have shown that only the radioactivity of [2-^{14}C]glycine, [2-^{14}C]glutamic acid, [1-^{14}C]glutamic acid, [2,3-$^{14}C_2$]-succinic acid and [1,4-$^{14}C_2$]succinic acid, sodium [1-^{14}C]-, [2-^{14}C]-, and [3-^{14}C]propionate, sodium [1-^{14}C]- and [2-^{14}C]acetate, [1,3-$^{14}C_2$]glycerol, [2-^{14}C]glycerol, [1-^{14}C]- and [2-^{14}C]-β-alanine, and of aspartic acid was utilized to any significant extent. Careful degradation has only been carried out in a few cases (Scheme 5).



Scheme 5. Degradation of ricinine *(57)*.

Thus, following administration of [2-^{14}C]glutamic acid, radioactivity is found primarily in C-8 [104, 108], while [1-^{14}C]glutamic acid and [1-^{14}C]acetate label preferentially carbon atoms 6 and 8 of ricinine, the absolute degree of incorporation of [1-^{14}C]acetate being greater than that of [1-^{14}C]glutamic acid [104, 108]. [3-^{14}C]Aspartic acid is incorporated very considerably; the radioactivity is found primarily in carbon atom 3 of the alkaloid [104].

The incorporation of [2-^{14}C]acetate into ricinine is even more extensive than that of [3-^{14}C]aspartic acid, most of the activity being localized in carbon atoms 2 or 3 [104, 108]. The author concludes from this that the immediate precursor of ricinine is likely to be a non-nitrogeneous C_4-acid (see below), which, however, does not give rise to carbon atoms 4 and 5 [104]. In the glyoxylic acid cycle, which along with the citric acid cycle plays a major role in *Ricinus* shoots [109], [2-^{14}C]acetate leads to a C_4-acid labelled in the 2- and 3-positions. The radioactivity of [1-^{14}C]- and [3-^{14}C]propionate is incorporated primarily into the nitrile carbon, while that of [2-^{14}C]propionate is localized primarily in the pyridone ring. This indicates that propionate is not incorporated directly into nicotinic acid but is catabolized to acetate [81] via β-oxidation and cleavage of the carboxyl group, and ends up in the citric acid cycle. It has been shown experimentally [108] that [1-^{14}C]- and [3-^{14}C]propionate correspond to [1-^{14}C]acetate.

[2,3-$^{14}C_2$]Succinic acid is incorporated to a relatively high degree, even higher than that of [2-^{14}C]acetate, the radioactivity being localized exclusively in the pyridone ring [107]. In the case of [1,4-$^{14}C_2$]succinic acid, which is incorporated to a lower degree, 25 % of the radioactivity are localized in the cyano group and 75 % in the pyridone ring.

After application of [1,3-$^{14}C_2$]glycerol preferably carbon atoms 4 and 6 became radioactive [108a], while after application of [2-^{14}C]glycerol radioactivity was located mainly in position 5 [108b].

Administration of [2-^{14}C]lysine resulted in [6-^{14}C]ricinine, while administration of α-amino[ε-^{14}C]adipic acid produced [2,6-$^{14}C_2$]ricinine [110]. Although unlabelled lysine led to an increased ricinine content in plants [111], other authors [104, 106] found that [2-^{14}C]lysine is incorporated to only a very small extent, so that this amino acid cannot be considered as a direct precursor.

It appears therefore that a C_4-acid such as succinic or aspartic acid as well as a C_3-compound such as glycerol are possible natural precursors, a finding that is in complete accord with the experiments on the biosynthesis of nicotinic acid.

f) Isopelletierine, Methylisopelletierine, and Pseudopelletierine

Isopelletierine *(59)*, methylisopelletierine *(60)*, and pseudopelletierine *(61)* are homologues of norhygrine, hygrine *(19)*, and tropinone *(1)* with a piperidine ring instead of the pyrrolidine ring; these alkaloids occur in the pomegranate tree, *Punica granatum*. Theoretically, they are derived from lysine [4]. Pseudopelletierine *(61)* has been synthetized in the same way as tropinone, except that glutardialdehyde was used instead of succindialdehyde [112]. This synthesis has also been achieved

[108] *R. A. Anwar, T. Griffith,* and *R. U. Byerrum,* Federat. Proc. *20,* 374 (1961).

[108a] *P. F. Juby* and *L. Marion,* Biochem. biophysic. Res. Commun. *5,* 461 (1961).

[108b] *J. Essery, P. F. Juby, L. Marion,* and *E. Trumbull,* J. Amer. chem. Soc. *84,* 4597 (1962).

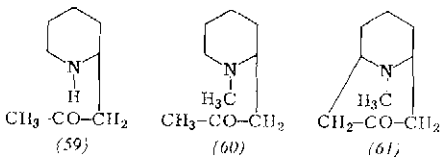
[109] *H. L. Kornberg* and *H. Beevers,* Nature (London) *180,* 35 (1957).

[110] *H. Tamir* and *D. Ginsburg,* J. chem. Soc. (London) *1959,* 2921.

[111] *O. V. Bogdashevskaja,* Dokl. Akad. Nauk SSSR *99,* 853 (1954).

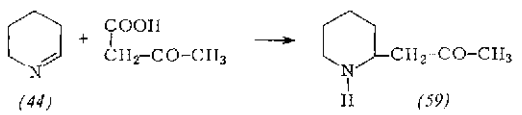
[112] *R. Ch. Menzies* and *R. Robinson,* J. chem. Soc. (London) *125,* 2163 (1924).

under physiological conditions [6]. Isopelletierine *(59)* has also been obtained under similar conditions. For this purpose, several authors [21, 113] started out from Δ^1-piperideine *(44)*. The chemistry of *(44)* has been



(59) *(60)* *(61)*

studied intensively by *Schöpf* [60]; it forms isopelletierine *(59)* by reacting with acetoacetic acid or acetonedicarboxylic acid. The fact that Δ^1-piperideine *(44)* may occur in the living cell was demonstrated above [*(42)* → *(44)*]. By analogy with the reactions leading to the corresponding pyrrolidine bases, isopelletierine *(59)* and



(44) *(59)*

methylisopelletierine *(60)* have also been obtained semienzymatically from cadaverine [23] or *N*-methylcadaverine [22], respectively, with the aid of diamine oxidase. The incorporation of [1,5-$^{14}C_2$]cadaverine into pelletierine alkaloids has been demonstrated in *Punica granatum* [114]. No degradation has yet been reported.

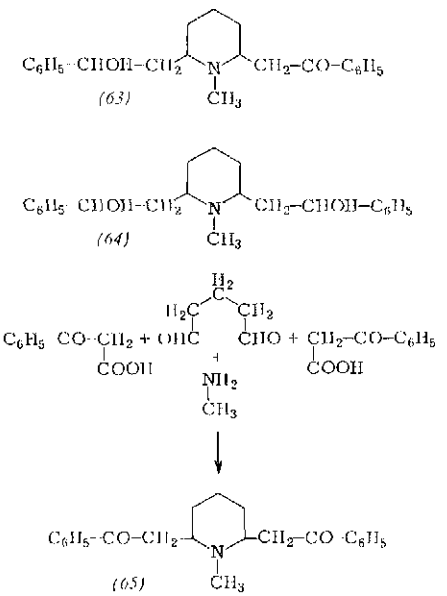
g) Coniine

Coniine *(62)*, the principal alkaloid of hemlock (*Conium maculatum*), is related structurally and therefore almost certainly biogenetically [4c] to isopelletierine *(59)*. It contains a methylene group instead of the carbonyl group of *(59)*. Uniformly labelled lysine gives rise to radioactive coniine [115]; this suggests that its biosynthesis proceeds via Δ^1-piperideine *(44)*.

(44) *(62)*

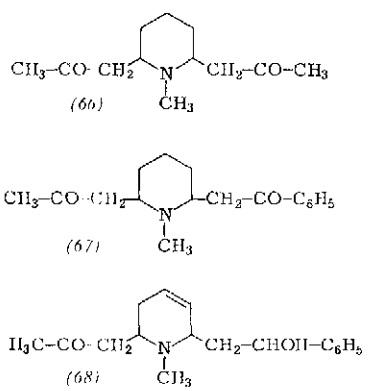
h) Lobeline, Lobelanidine, and Lobelanine

The alkaloids of *Lobelia inflata* are also structurally related to pelletierine. The most important of these are lobeline *(63)*, lobelanidine *(64)*, and lobelanine *(65)*. The first two are reduction products of lobelanine. The latter was synthetized in 80% yield from glutardialdehyde, methylamine, and 2 moles of benzoylacetic acid by *Schöpf* et al. [6] under physiological conditions (2 days at 25 °C and pH 4). If a mixture of benzoylacetic acid and acetoacetic acid is used during the synthesis instead of benzoylacetic acid alone, then not only the two symmetrical bases diphenyl-lobelidione *(65)* and dimethyl-lobelidione *(66)* are obtained, but also the unsymmetrical derivative 8-methyl-10-phenyl-lobelidione *(67)* [116, 117]. The alkaloid sedinine *(68)*, for example, which occurs in *Sedum acre*, can be derived from *(67)*.



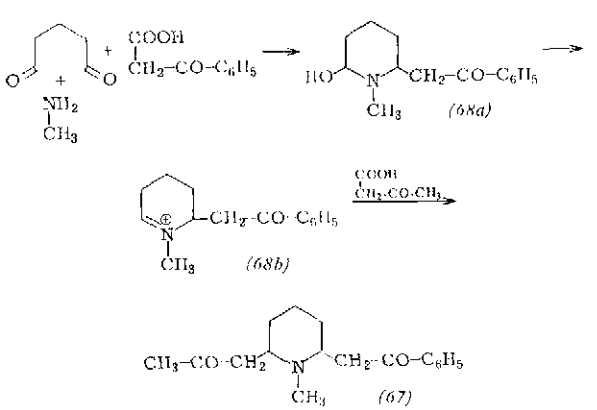
(63) *(64)* *(65)*

Franck [116] managed to synthetize 8-methyl-10-phenyl-lobelidione *(67)* in two stages under physiological conditions, and has interpreted his result as indicat-



(66) *(67)* *(68)*

ing that the simply substituted intermediate *(68)* is sufficiently stable to become concentrated in another part of the plant, where reaction with a second molecule of a β-keto acid can take place.



(68a) *(68b)* *(67)*

[113a] *Cl. Schöpf, F. Braun, K. Burkhardt, G. Dummer*, and *H. Müller*, Liebigs Ann. Chem. *626*, 123 (1959).

[113b] Cf. also *Cl. Schöpf*, Angew. Chem. *69*, 69 (1957).

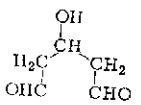
[114] *H. W. Liebisch, H. R. Schütte*, and *K. Mothes*, unpublished results.

[115] *U. Schiedt* and *H. G. Höss*, Z. Naturforsch. *13b*, 691 (1958).

[116] *B. Franck*, Chem. Ber. *93*, 2360 (1960).

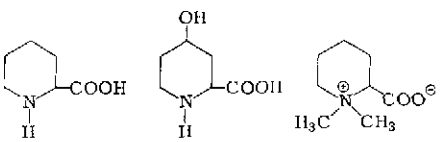
[117] *Cl. Schöpf* and *Th. Kauffmann*, Liebigs Ann. Chem. *608*, 88 (1957).

This would explain why only unsymmetrically substituted lobelidione derivatives have been found in *Sedum acre* [118]. However, it is more likely, that although these reactions can proceed spontaneously, they are actually enzymatically controlled. β-Hydroxyglutardialdehyde *(69)*, which is a possible precursor of sedinine, cannot be condensed with benzoylacetic acid and methylamine under physiological conditions, so that this aldehyde appears to be a questionable biosynthetic intermediate [119]. It is possible that the presynthetized piperidine ring is oxidized specifically to the



(69)

hydroxy compound, as has been shown to occur in the biosynthesis of 4-hydroxypipecolinic acid *(71)* from pipecolinic acid *(70)* [120]. This could then form the unsaturated compound sedinine by elimination of water. Hydroxy compounds of this type have been shown to occur in *Lobelia inflata* [117].

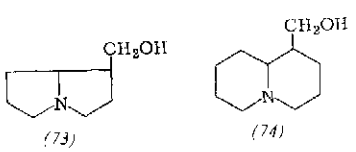


(70) *(71)* *(72)*

By analogy to the experiments with stachydrine *(25)*, two-weeks-old alfalfa plants do not incorporate [2-^{14}C]-lysine in homostachydrine *(72)* [121], the betaine of pipecolinic acid, although lysine may give rise to pipecolinic acid [122]. It is possible that incorporation may occur in older plants as in the case of stachydrine.

4. Pyrrolizidine and Quinolizidine Alkaloids

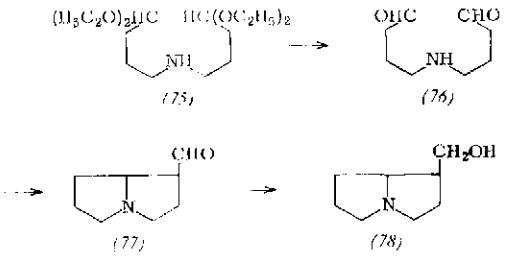
The pyrrolizidine and quinolizidine alkaloids have homologous structures. This is shown by comparison of laburnine *(73)* as a representative pyrrolizidine derivative and lupinine *(74)* as an example of the quinolizidines.



(73) *(74)*

a) Pyrrolizidine Alkaloids of the Laburnine Type

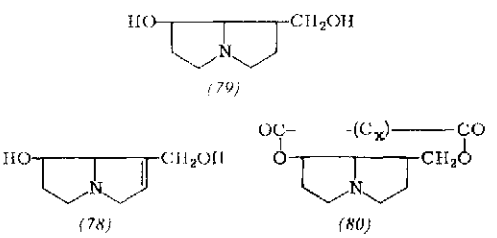
The pyrrolizidine alkaloids apparently belong to the ornithine family. This amino acid is said to give rise to the skeleton of the pyrrolizidine alkaloids *(73)* via an iminodialdehyde *(76)* [4c, 123]. Accordingly, it has proved possible to carry out a synthesis of the pyrrolizidine ring system under physiological conditions via this biosynthetic pathway [124]. At pH 7, the iminodialdehyde *(76)* formed a pyrrolizidine derivative *(77)* from the corresponding acetal *(75)* within seven days. Hydrogenation of *(77)* gave a mixture of stereoisomeric 1-hydroxymethylpyrrolizidines *(73)* [laburnine and trachelanthamidine] in 52% yield. With [2-^{14}C]ornithine in *Crotalaria spectabilis* reactive monocrotaline was obtained, the radioactivity of which was located almost exclusively in the retronecine *(78)* [125].



(75) *(76)* *(77)* *(78)*

b) Retronecine and Platynecine Bases

The diversity of the pyrrolizidine alkaloids, especially those from *Senecio* or *Crotalaria* species, is much more interesting than that of the simple pyrrolizidine alkaloids of the laburnine type *(73)*. Many are derived from retronecine *(78)* or platynecine *(79)* and, as shown in formula *(80)*, are esterified with dicarboxylic acids with chains containing 5, 6, 7, 8, or 10 carbon atoms.



(79) *(78)* *(80)*

By analogy to the synthesis of laburnine *(73)* from ornithine, it is assumed that these retronecine and platynecine bases are formed from hydroxyornithine [4c], which, so far as we know, has not yet been found in nature but which might originate from 2-hydroxyglutamic acid; the latter has been found to occur in proteins. This would be similar to the synthesis of ornithine from glutamic acid. However, the incorporation of [^{14}C]-ornithine into *Crotalaria* alkaloids indicates a subsequent oxidation step, similar to that assumed to occur with the unsaturated *Sedum* alkaloids (see above) and 4-hydroxypipecolinic acid.

c) Necinic Acids

Little work has been reported on the biosynthesis of the necinic acids, the acid components of the esterified pyrrolizidine alkaloids. It is assumed [126] that these acids

[118] *B. Franck*, Chem. Ber. *91*, 2803 (1958).

[119] *B. Franck* and *M. Schiebel*, Naturwissenschaften *48*, 717 (1961).

[120] *W. Schenk*, *H. R. Schütte*, and *K. Mothes*, Flora *152*, 590 (1962).

[121] *A. V. Robertson* and *L. Marion*, Canad. J. Chem. *37*, 1043 (1959).

[122] *P. H. Lowy*, Arch. Biochem. Biophysics *47*, 228 (1953); *L. Fowden*, J. exp. Bot. (London) *11*, 302 (1960).

[123] *Cl. Schöpf*, Chimia *2*, 206, 240 (1948).

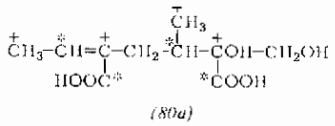
[124] *N. J. Leonard* and *St. W. Blum*, J. Amer. chem. Soc. *82*, 503 (1960); *K. Babor*, *I. Jezo*, *V. Kalac*, and *M. Karvas*, Chem. Zvesti *13*, 163 (1959); Chem. Zbl. *133*, 5300 (1962).

[125] *E. Nowacki* and *R. U. Byerrum*, Life Sciences *5*, 157 (1962).

[126] *R. Adams* and *M. Gianturco*, Angew. Chem. *69*, 5 (1957).

result from repeated condensations of acetate residues either alone or with simple C_3-residues.

[1-^{14}C]Acetate and [2-^{14}C]acetate are in fact incorporated well into the retronecinic acid *(80a)* portion of the alkaloid retrorsine by *Senecio isatideus*, while [2-^{14}C]-mevalonic acid shows practically no incorporation under the same conditions [127]. Degradation of the acid *(80a)* by Kuhn-Roth oxidation, oxidation with lead tetraacetate and ozonization showed that four molecules of acetate are used in its synthesis. Formula *(80a)* shows the distribution of radioactivity following incorporation of [1-^{14}C]acetate (asterisks) and [2-^{14}C]acetate (crosses). On the basis of these experiments, the authors concluded that this type of acid is built up from two molecules of acetoacetic acid, each of which is first condensed with a C_1-residue. The formation of various necinic acids may be explained by assuming different condensations of this C_5-residue (acetoacetic acid + C_1) either with another C_5-residue or a propionic acid moiety [127]. However, the result can also be explained by assuming that one molecule of acetate condenses with one molecule of malonate to form the C_5-residue.

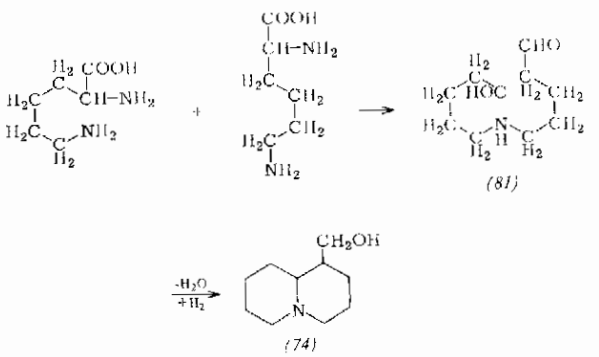


(80a)

Crotalaria spectabilis incorporates [1-^{14}C]acetate and [1-^{14}C]propionate mainly into the corresponding necinic acid [125].

d) Lupin Alkaloids

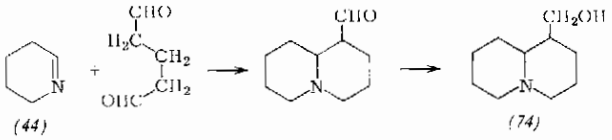
The alkaloids from lupins belong to the lysine family. *Schöpf* [4c, 128] postulated as early as 1931 that lupinine *(74)* arises from two molecules of lysine or its biochemical equivalent by way of an iminodialdehyde *(81)*. This



(81)

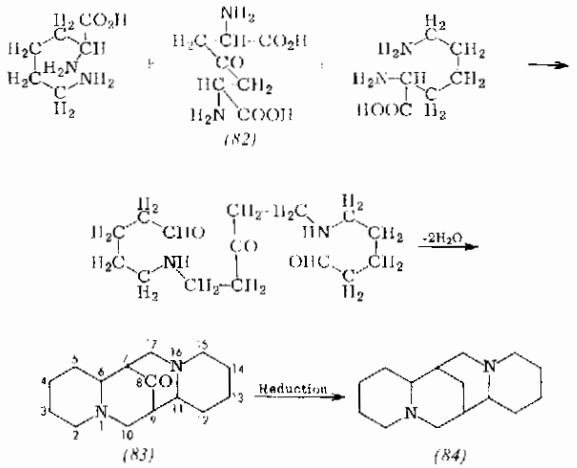
(74)

synthesis has since been carried out successfully in the laboratory [129]. However, *Schöpf* [5a] also suggested the possibility of a biosynthesis of lupinine from Δ^1-piperideine *(44)* and a C_5-residue such as glutardialdehyde or its α-carboxy derivative.



(44) *(74)*

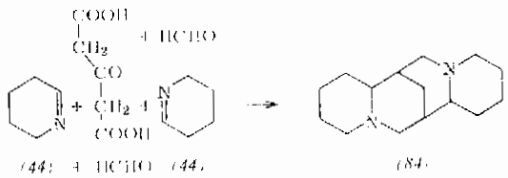
The synthesis of sparteine *(84)*, which consists of two quinolizidine rings, has been assumed [4c] to involve either three molecules of lysine or two molecules of lysine and one molecule of 4-keto-2,6-diaminopimelic acid *(82)*. The reaction presumably occurs via 8-keto-sparteine *(83)* [130].



(82)

(83) *(84)*

A corresponding synthesis under physiological conditions from ω-aminovaleraldehyde, acetonedicarboxylic acid, and formaldehyde [131] could not at first be confirmed [132], but has recently been accomplished from Δ^1-piperideine *(44)*, acetonedicarboxylic acid, and formaldehyde under changed conditions [113b], although actually the stereoisomer α-isosparteine resulted after



(44) *(84)*

reduction of the ketone initially formed. A laboratory synthesis in conformance with the above biosynthetic pathway has also been carried out [133].

Oxidized lupin alkaloids of the sparteine type, such as lupanine *(85)*, hydroxylupanine *(86)*, and anagyrine *(87)*, can be considered as arising by oxidation of sparteine *(84)*. On the other hand, cytisine *(88)*, rhombifoline *(89)*, and possibly angustifoline *(90)* are also regarded as oxidation products of sparteine [4c]. *N*-Methylcytisine *(91)* is definitely formed in plants by methylation of the secondary amino group of cytisine; this

[127] *C. Hughes* and *F. L. Warren*, J. chem. Soc. (London) *1962*, 34.

[128] *Cl. Schöpf*, Liebigs Ann. Chem. *465*, 97 (1928); *Cl. Schöpf*, *E. Schmidt*, and *W. Braun*, Ber. dtsch. chem. Ges. *64*, 683 (1931).

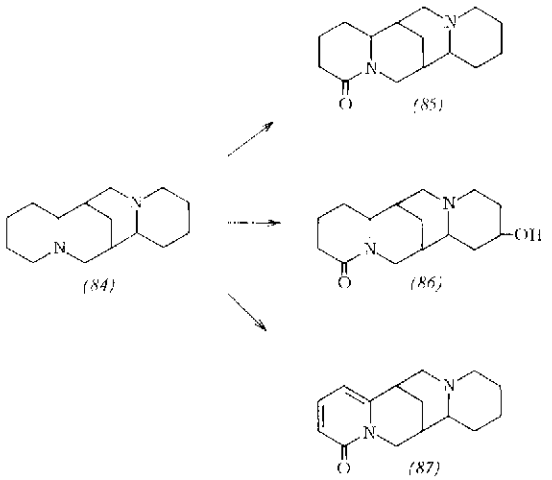
[129] *E. E. van Tamelen* and *R. L. Foltz*, J. Amer. chem. Soc. *82*, 502 (1960).

[130] *E. Wenkert*, Experientia *15*, 165 (1959).

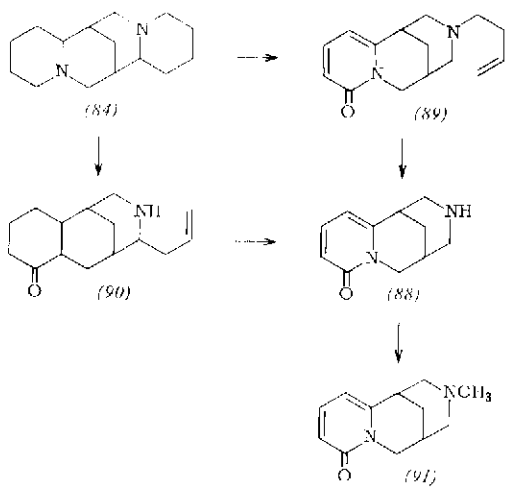
[131] *E. Anet*, *G. K. Hughes*, and *E. Ritchie*, Nature (London) *165*, 35 (1950).

[132] *Cl. Schöpf*, *G. Benz*, *F. Braun*, *H. Hinkel*, and *R. Rokohl*, Angew. Chem. *65*, 161 (1953).

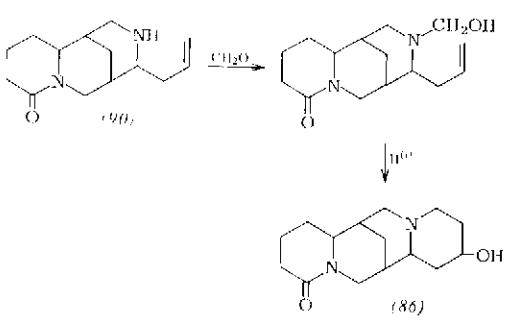
[133] *E. E. van Tamelen* and *R. L. Foltz*, J. Amer. chem. Soc. *82*, 2400 (1960).



transformation, which takes place intensively in the shoots of *Cytisus laburnum*, is interpreted as a detoxification reaction, since the young plants are quite sensitive to cytisine, but are insensitive to methylcytisine [134].

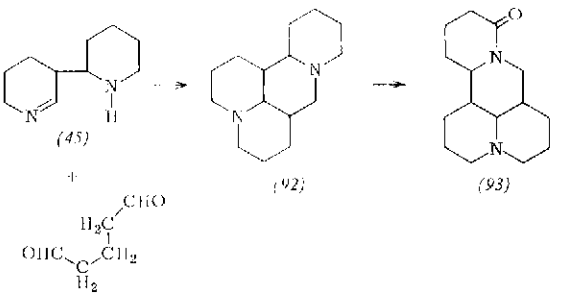


It has also been suggested that angustifoline is transformed into lupanine biosynthetically. Both of these alkaloids occur together in *Lupinus angustifolius* and other lupins; moreover, angustifoline *(90)* reacts with formaldehyde *in vitro* under physiological conditions to

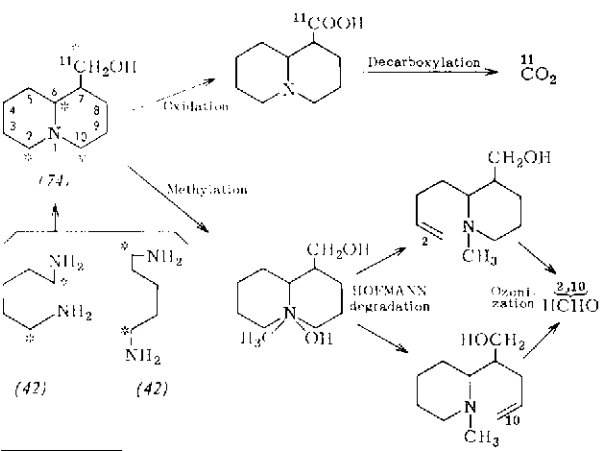


form hydroxylupanine *(86)* (actually epihydroxylupanine) [135]. However, neither sodium [^{14}C]formate nor [^{14}C]formaldehyde is incorporated into hydroxylupanine and lupanine by *L. angustifolius* [136] to any significant extent. Epihydroxylupanine has recently been discovered in *Ormosia jamaicensis* [137].

Matrine *(93)*, another *Papilionaceae* alkaloid, is an isomer of lupanine. *Schöpf* [60, 138] has postulated that tetrahydroanabasine *(45)*, which, together with one molecule of glutardialdehyde, can give rise to the matrine skeleton *(92)*, is an intermediate in the biogenesis of matrine. [1,5-$^{14}C_2$]Cadaverine and [2-^{14}C]lysine have



in fact been found to be incorporated extensively into lupinine [139, 140], sparteine [139–141], lupanine [142, 143], hydroxylupanine [142], matrine [144], and methylcytisine [144]. After administration of [1,5-$^{14}C_2$]cadaverine *(42)*, degradation of the lupinine *(74)* obtained revealed that carbon atoms 2, 10, and 11 each contained one-quarter of the total radioactivity of the alkaloid [140, 145], so that the distribution of radioactivity is probably that shown by the asterisks in *(74)*; according to this pathway, the lupinine in *Lupinus luteus* can arise from two molecules of cadaverine *(42)*. As illustrated



[136] *H. R. Schütte, E. Nowacki,* and *Ch. Schäfer,* unpublished results.

[137] *C. H. Hassall* and *E. M. Wilson,* Chem. and Ind. *1961*, 1358.

[138] *Cl. Schöpf, H. Arm, G. Benz,* and *H. Krimm,* Naturwissenschaften *38*, 186 (1951).

[139] *H. R. Schütte* and *E. Nowacki,* Naturwissenschaften *46*, 493 (1959).

[140] *H. R. Schütte,* Arch. Pharmaz., Ber. dtsch. pharmaz., Ges. *293*, 1006 (1960).

[141] *F. Jaminet,* Pharmazie *15*, 194 (1960).

[142] *H. R. Schütte, E. Nowacki,* and *Ch. Schäfer,* Arch. Pharmaz., Ber. dtsch. pharmaz. Ges. *295*, 20 (1962).

[143] *E. Nowacki* and *R. U. Byerrum,* Biochem. Biophys. Res. Commun. *7*, 58 (1962).

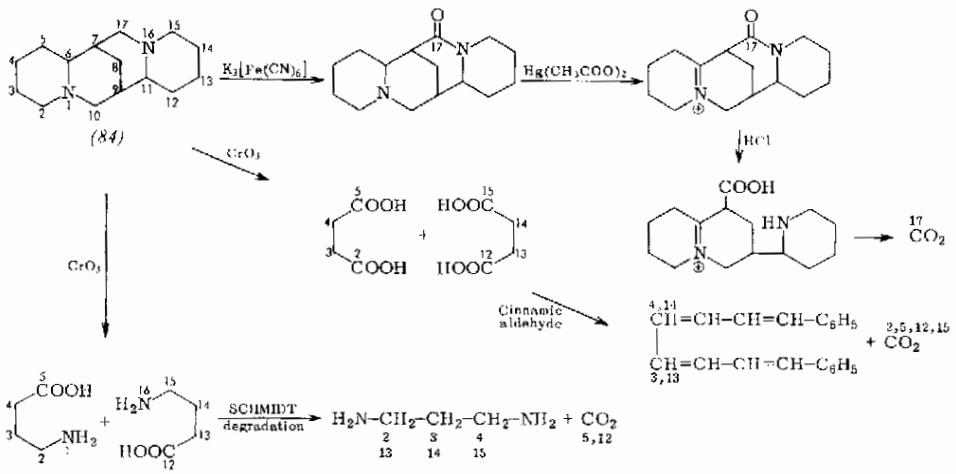
[144] *H. R. Schütte, H. Aslanow,* and *Ch. Schäfer,* Arch. Pharmaz., Ber. dtsch. pharmaz. Ges. *295*, 34 (1962).

[145] *M. Soucek* and *H. R. Schütte,* Angew. Chem. *74*, 901 (1962).

[134] *M. Pöhm,* Mh. Chem. *90*, 58 (1959).

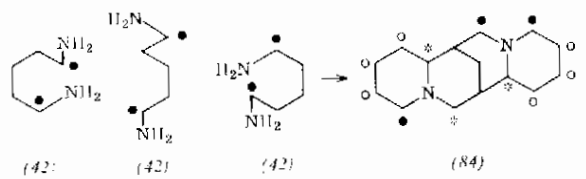
[135] *F. Bohlmann* and *E. Winterfeldt,* Chem. Ber. *93*, 1956 (1960).

in Scheme 6, the distribution of the radioactivity in nine of the fifteen carbon atoms of sparteine *(84)* was investigated [146]; the results are shown in Scheme 7.



Scheme 6. Degradation of sparteine *(84)*.

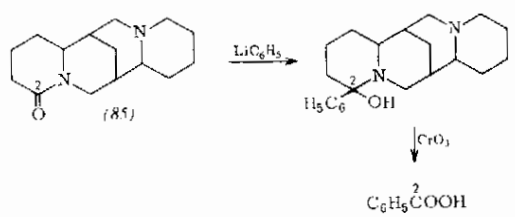
Each of the three radioactive carbon atoms contained one-sixth of the total radioactivity of the sparteine. If the residual activity is assumed to be distributed according to the asterisks in Scheme 7, the biosynthesis of sparteine *(84)* from three molecules of cadaverine *(42)* can be understood.



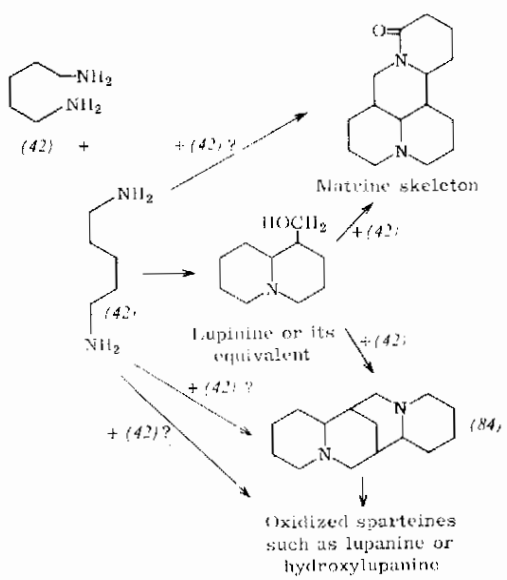
Scheme 7. Distribution of the radioactivity in sparteine *(84)* after biosynthesis from [1,5-$^{14}C_2$]cadaverine *(42)*.

● radioactive; ○ inactive; * probable residual activity.

After administration of [1,5-$^{14}C_2$]cadaverine *(42)*, the carbonyl groups of lupanine *(85)* [142], hydroxylupanine *(86)* [142], and matrine *(93)* [144] were isolated as the carboxyl group of benzoic acid with the aid of phenyl-lithium and subsequent oxidation.



In each case, this benzoic acid contained one-sixth of the specific activity of the lupanine, hydroxylupanine, and matrine. The succinic acid obtained from lupanine after oxidation with chromic acid, by analogy to the degradation of sparteine, also contained one-sixth of the radioactivity of the original alkaloid [147]; hence, it may also be assumed that these compounds have been biosynthetized from three molecules of cadaverine. If it is taken into consideration that, in *L. angustifolius*, [^{3}H]sparteine yields radioactive lupanine and hydroxylupanine, whereas [^{3}H]lupanine yields only radioactive hydroxylupanine [148], and that *L. luteus* can transform [^{14}C]lupinine into sparteine to some extent, whereas sparteine is not a precursor of lupinine [149], then on the basis of what is already known, Scheme 8 can be constructed to account for the biosynthesis of the *Lupinus* and *Papilionaceae* alkaloids. The only question that remains is whether the formation of cadaverine is a necessary step in the biosynthesis from lysine.



Scheme 8. Biosynthesis of *Papilionaceae* alkaloids.

Received, January 28th, 1963 [A 284/99 IE]
German version: Angew. Chem. 75, 265 (1963).

[146] *H. R. Schütte, F. Bohlmann*, and *W. Reusche*, Arch. Pharmaz., Ber. dtsch. pharmaz. Ges. *294*, 610 (1961).

[147] *H. R. Schütte* and *Ch. Schäfer*, Naturwissenschaften *48*, 669 (1961).

[148] *H. R. Schütte, E. Nowacki, H. P. Kovacs*, and *H. W. Liebisch*, Arch. Pharmaz., Ber. dtsch. pharmaz. Ges. *296* (1963), in the press.

[149] *H. R. Schütte*, Atompraxis 7, 91 (1961).

Methods of Peptide Synthesis[*]

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Dedicated to Dr. W. Foerst on the occasion of his 60th birthday

In the series of accounts of progress in the field of peptide synthesis, this review surveys the literature from the beginning of 1959 to the middle of 1962.

Introduction
Protecting groups
  Protecting group on the nitrogen
  Protecting group on the carboxyl group
Methods of coupling
  Use of chlorides
  Use of hydrazides and azides
  Use of unsaturated compounds
  Use of activated esters
  Use of phosphorus derivatives
  Use of azoles
  Sundry methods
  Synthesis of cyclic peptides
Racemization during the formation of peptides

Introduction

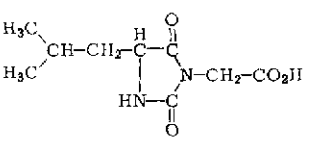
At the time of a previous review of peptide syntheses [1], the chemistry of polypeptide hormones was gradually being disclosed. In order to be able to build longer chains from polyfunctional amino acids, attempts have been made in recent years to find new protecting groups which can be removed in a specific manner, to raise the yields of the coupling reactions, and to avoid racemization of the natural amino acids. These efforts have led, for example, to the synthesis of corticotrophic peptides with the sequence of the first twenty-three [2] and twenty-four [3] amino acids of natural corticotrophin. Further accounts of the problems involved in peptide syntheses [4–6] have since been added to those cited [1].

Protecting Groups

Protecting Group on the Nitrogen

The groups described below may be used for protecting not only nitrogen, but also hydroxyl and mercapto groups, mostly by methods that are similar in principle[7].

On saponification of dipeptide esters with alkali, the carbobenzoxy group – which is probably still used most – leads more or less easily to the formation of urea derivatives [8]. *MacLaren* [9] has recently investigated this troublesome reaction thoroughly. He found that carbobenzoxy-dipeptide esters in which the ester group was attached to glycine rearranged in the cold if excess alkali was used. For example, the ethyl ester of carbobenzoxyglycylleucine can be hydrolysed with 2 moles of alkali to give the carbobenzoxy-dipeptide without any trouble, whereas the ethyl ester of carbobenzoxyleucylglycine gives a difficultly soluble hydantoin derivative *(1)* under these conditions.



(1)

Birkofer and coworkers [10] were able to remove the carbobenzoxy residue by hydrogenation with triethylsilane [11] in the presence of catalytic quantities of $PdCl_2$ and triethylamine. They refluxed the carbobenzoxy derivative in this solution for several hours and then decomposed the resulting silyl derivative with methanol to give the free amino acid or peptide. These conditions also allow hydrogenolysis of benzyl esters; benzyl linked to sulfur is unaffected.

Substituted carbobenzoxy groups enjoy increasing popularity because of the gradation of reactivity which

[*] Communication No. 28 in the series "Über Peptidsynthesen" (On peptide syntheses); Communication No. 27: *T. Wieland, H. Determann,* and *W. Kahle,* Angew. Chem. internat. Edit. *2*, 154 (1963). Peptide Syntheses IV: *T. Wieland,* Angew. Chem. *71*, 417 (1959).

[1] *T. Wieland,* Angew. Chem. *63*, 7 (1951); *ibid. 66*, 507 (1954); *T. Wieland* and *B. Heinke*, ibid. *69*, 362 (1957); *T. Wieland, ibid. 71*, 417 (1959).

[2] *K. Hofmann, H. Yajika, N. Yanaihara, T. Y. Liu,* and *S. Lande,* J. Amer. chem. Soc. *83*, 487 (1961).

[3] *H. Kappeler* and *R. Schwyzer,* Helv. chim. Acta *44*, 1136 (1961).

[4] *J. P. Greenstein* and *M. Winitz:* Chemistry of the Amino Acids. Wiley, New York 1961.

[5] *E. Bricas,* Bull. Soc. chim. France *1961*, 2001.

[6] *N. F. Albertson,* Org. Reactions *12*, 157 (1962).

[7] See *H. C. Beyerman* and *J. S. Bontekoe,* Proc. chem. Soc. (London) *1961*, 249.

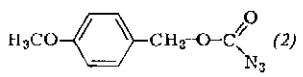
[8] *F. Wessely* and *E. Kornn,* Hoppe-Seylers Z. physiol. Chem. *174*, 306 (1928); *F. Wessely, K. Schlögel,* and *G. Korger,* Nature (London) *169*, 708 (1952); *F. Wessely, K. Schlögel,* and *E. Wawersich,* Mh. Chem. *83*, 1426 (1952).

[9] *J. A. MacLaren,* Austral. J. Chem. *11*, 360 (1958).

[10] *L. Birkhofer, E. Bierwirth,* and *A. Ritter,* Chem. Ber. *94*, 821 (1961).

[11] *J. W. Jenkins* and *H. W. Post,* J. org. Chemistry *15*, 556 (1950).

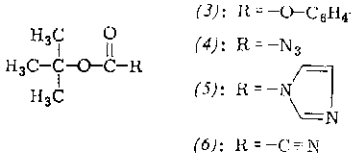
may be achieved. The nitro group in the *p*-nitrobenzyloxycarbonyl (PNZ) group reduces the electron density at the benzyl carbon atom and hence makes re-elimination of the group with HBr in glacial acetic acid difficult. On the other hand, the PNZ group is removed by catalytically activated hydrogen much more readily than the carbobenzoxy group [12]. These differences have made it possible to prepare prolyl-*N*(ε)-PNZ-lysine from the carbobenzoxy compound [13]. The effect of a methoxyl group is in the opposite sense; it considerably facilitates proton-catalysed removal of the *p*-methoxybenzyloxycarbonyl (PMZ) group [14]. Introduction of the PMZ group has been accomplished by *Weygand* and *Hunger* [15] using the crystalline azide *(2)*; anhydrous



(2)

trifluoroacetic acid at 0 °C is sufficient to split it off. The carbobenzoxy residue is not removed under these conditions; it requires boiling for 30 minutes with trifluoroacetic acid [16]. A phenol must be added in order to capture the benzyl cation and prevent side reactions. For the use of the *p*-chlorobenzyloxycarbonyl group, see [17].

Increased importance has been attained by the t-butyloxycarbonyl (BOC) group, which at the time of the previous review [1] could only be introduced by reaction of the isocyanate compounds with t-butanol. Several more elegant ways have since been devised. First, the preparation of t-butyl-*p*-nitrophenylcarbonate *(3)* was reported; this reacts with amino acids within 20 minutes in the presence of alkali at 100 °C [18]. Acylation can be carried out under milder conditions with t-butoxycarbonylazide *(4)* [20], which was made for the first time by *Carpino* [19]. The imidazolide *(5)* [21] and the cyanide *(6)* [22] may also be used for simple syntheses of



(3): R = $-O-C_6H_4-NO_2$
(4): R = $-N_3$
(5): R =
(6): R = $-C\equiv N$

[12] *C. Berse, R. Boucher,* and *L. Piché,* J. org. Chemistry *22,* 805 (1957).

[13] *J. E. Shields* and *F. H. Carpenter,* J. Amer. chem. Soc. *83,* 3066 (1961).

[14] *F. C. McKay* and *N. F. Albertson,* J. Amer. chem. Soc. *79,* 4686 (1957).

[15] *F. Weygand* and *K. Hunger,* Chem. Ber. *95,* 1 (1962).

[16] *F. Weygand* and *W. Steglich,* Z. Naturforsch. *14b,* 472 (1959).

[17] *L. Kisfaludy* and *S. Dualszky,* Acta. chim. Acad. Sci. Hungary *24,* 301 (1960); *ibid. 24,* 309 (1960); Chem. Abstr. *55,* 9295 (1961).

[18] *G. W. Anderson* and *A. C. McGregor,* J. Amer. chem. Soc. *79,* 6180 (1957).

[19] *L. A. Carpino,* J. Amer. chem. Soc. *79,* 98, 4427 (1957); *L. A. Carpino, C. A. Giza,* and *B. A. Carpino,* J. Amer. chem. Soc. *81,* 955 (1959); see also [20].

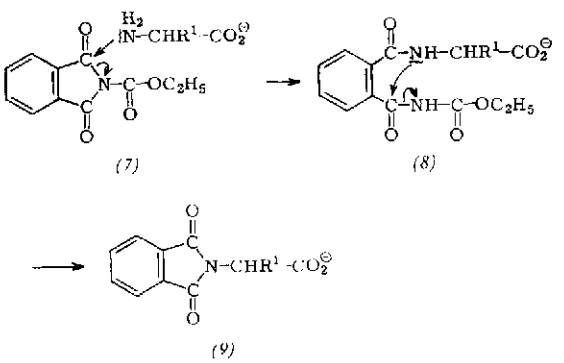
[20] *R. Schwyzer, P. Sieber,* and *H. Kappeler,* Helv. chim. Acta *42,* 2622 (1959).

[21] *W. Klee* and *M. Brenner,* Helv. chim. Acta *44,* 2151 (1961).

[22] *L. A. Carpino,* J. Amer. chem. Soc. *82,* 2725 (1960).

BOC derivatives. The BOC group can be split off at room temperature by the procedure of *Anderson* and *McGregor* [18] using HBr in diethyl phosphite or glacial acetic acid, or – separately from the carbobenzoxy group – by the method of *Schwyzer* [23] using anhydrous trifluoroacetic acid. The BOC group is not removed by acetic acid, so that it is possible to split it off separately if a trityl group is also present [24].

The phthalyl group is being used less and less on account of its sensitivity to alkali, which has recently been measured quantitatively [25]. Moreover, the commonly used cleavage with excess hydrazine hydrate in alcohol cannot be applied to base-sensitive peptides. In this respect, *Schwyzer* and coworkers [26] have made the valuable observation that hydrazine is effective even in weakly acid solution. We have observed that the phthalyl group can be removed very easily by heating with imidazole and a little water. Its introduction is now performed at room temperature within 15 minutes using *N*-ethoxycarbonylphthalimide *(7)* according to *Nefkens* [27]. The triacylamide *(7)* undergoes ring opening to give a diacylamide *(8)*, which splits off urethane and gives the phthalylamino acid *(9)*. Phthalyl-



(7) *(8)* *(9)*

ation of amino acids is also possible by heating with diphenyl phthalate [28]. The trifluoroacetyl (TFA) group can be introduced in a similar way [29].

N-Formylamino acids are particularly prone to racemization during peptide syntheses [30]. Despite this, attention should be paid to a method for specific removal of the formyl group by oxidation with 15 % aqueous hydrogen peroxide at 60 °C for 2 hours [31]. Oxidation with peroxybenzoic acid is a mild way of splitting off the ethylthioformyl group, $C_2H_5-S-CO-$. A large number of amino acid and peptide derivatives

[23] *R. Schwyzer, W. Rittel, H. Kappeler,* and *B. Iselin,* Angew. Chem. *72,* 915 (1960).

[24] *R. Schwyzer* and *W. Rittel,* Helv. chim. Acta *44,* 159 (1961).

[25] *J. Rudinger, J. Krupička, M. Zaoral,* and *W. Cernick,* Collect. czechoslov. chem. Commun. *25,* 3338 (1960).

[26] *R. Schwyzer, A. Costopanagiotis,* and *P. Sieber,* Chimia *16,* 295 (1962).

[27] *G. H. L. Nefkens,* Nature (London) *185,* 309 (1960); *G. H. L. Nefkens, G. J. Tesser,* and *R. J. Nivard,* Recueil Trav. chim. Pays-Bas *79,* 688 (1961).

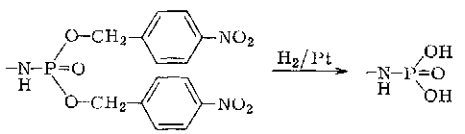
[28] *F. Weygand* and *J. Kaelicke,* Chem. Ber. *95,* 1031 (1962).

[29] *F. Weygand* and *A. Röpsch,* Chem. Ber. *92,* 2095 (1959).

[30] *J. C. Sheehan* and *D. H. Yang,* J. Amer. chem. Soc. *80,* 1154 (1958).

[31] *G. Losse* and *W. Zönnchen,* Angew. Chem. *72,* 385 (1960); Liebigs Ann. Chem. *636,* 140 (1960).

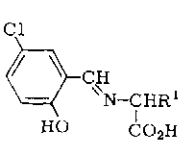
have been made recently in this way [32]. Dibenzylphosphoryl chlorides substituted in the *p*-position, particularly the *p*-nitro compound, allow introduction of phosphoric ester groupings, which may be re-eliminated from the nitrogen by catalytic hydrogenation. During their removal, *N*-phosphoryl derivatives that are extremely labile to acids are formed as intermediates [33]. The behavior of benzyl derivatives has been



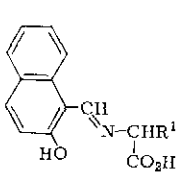
investigated further [34]. All benzyl residues may be removed from benzyl esters of dibenzylamino acids or of peptides by treatment for 7 days with glacial acetic acid saturated with HBr. The β-cyanoethyl group, $NC-CH_2-CH_2-$, formed by addition of amino acids onto acrylonitrile [35], is transferred over to aniline or other amines on heating [36]. *Turba* and coworkers [37] recently worked out an interesting method for hydrogenolytic release of amines and peptides from their 2,4-dinitrophenyl derivatives. Large amounts of a platinum catalyst are used; *m*-phenylenediamine is formed from the dinitrophenyl residue.

The *o*-nitrophenylmercapto group, $o\text{-}O_2N-C_6H_4-S-$, which is easily removed from the nitrogen with weak acids, may be introduced by treating the sodium salts or esters of amino acids with *o*-nitrophenylsulfenyl chloride [38].

As the benzylidene group was used only in preliminary work as a protecting group for peptide synthesis [39], and since its extreme lability to acid did not give rise to any great hopes, the more stable hydrogen bonded *o*-hydroxyarylidene compounds *(10a)* and *(10b)*, synthetized by *McIntire* [40], have been used of late [41]. Starting from the more stable naphthylidene-



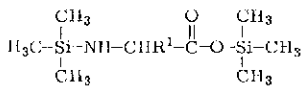
(10a)



(10b)

amino acids (type *10b)*, peptides were prepared in good yields using dicyclohexylcarbodiimide, the protective groups being split off with dilute mineral acid. The reaction products of amino acids with 1,3-dicarbonyl compounds (*e.g.* acetoacetic ester, benzoylacetone, 2,4-dioxopentane) are also hydrogen-bonded stable Schiff-bases. They can be used in peptide syntheses, the protecting group being split off by dilute acids after coupling [41a].

A substituent which has been closely examined recently is the trimethylsilyl group. *N*-Trimethylsilylamino esters are obtained from trimethylchlorosilane and amino esters [42]. The chloride reacts with salts of amino acids to give trimethylsilyl *N*-trimethylsilylamino esters *(11)*



(11)

[43], which are also formed from the sodium salts [44] or hydrochlorides [45] with trimethylsilyldiethylamine, diethylamine being eliminated. These esters are also formed with particular ease from free amino acids by warming them in hexamethylsilazane, $(H_3C)_3Si-NH-Si(CH_3)_3$, ammonia being evolved [46]. The silyl ester of the trimethylsilylamino acid may be acylated on the nitrogen with carbobenzoxyamino acids by the phosphorus oxychloride method [47] or by carbonyldiimidazole [48], the silyl group having no adverse effects. On working up, the carbobenzoxypeptide is obtained directly owing to the extreme sensitivity to water of the trimethylsilyl group [49]. Thus, the trimethylsilyl group has the function here of protecting the carboxyl group and not the nitrogen.

Protecting Groups on the Carboxyl Group

The carboxyl groups of *N*-acylamino acids may also be substituted with the trimethylsilyl group if the salts of the acids are treated with trimethylchlorosilane [50] or hexamethylsilazane. The trimethylsilyl ester is probably the most easily hydrolysable ester.

Tertiary butyl esters have become easily accessible in the last few years and are particularly useful. The t-butyl group, first used by *Sheehan* in the total synthesis of peni-

[32] *A. Hajós*, Chem. Ber. *94*, 2350 (1961).

[33] *A. Cosmatos, J. Photaki*, and *L. Zervas*, Chem. Ber. *94*, 2644 (1961).

[34] *K. T. Poroshin* and *V. I. Maksimov*, Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk *1960*, 1702; Chem. Abstr. *55*, 9292 (1961); *V. I. Maksimov* and *K. T. Poroshin, ibid. 1961*, 186; Chem. Abstr. *55*, 20984 (1961).

[35] *H. A. Bruson*, Org. Reactions *5*, 79 (1949).

[36] *P. F. Butskus* and *G. I. Denis*, Zhur. Obschei Khim. *30*, 1317 (1960); Chem. Abstr. *55*, 405 (1961); see also Chem. Abstr. *55*, 1460, 24583 (1961).

[37] *H. Fasold, G. Steinkopf*, and *F. Turba*, Biochem. Z. *335*, 1 (1961).

[38] *J. Goerdeler* and *A. Holst*, Angew. Chem. *71*, 775 (1959).

[39] *T. Wieland* and *W. Schäfer*, Liebigs Ann. Chem. *576*, 104 (1952).

[40] *F. C. McIntire*, J. Amer. chem. Soc. *69*, 1377 (1947).

[41] *J. C. Sheehan* and *W. J. Grenda*, J. Amer. chem. Soc. *84*, 2417 (1962).

[41a] *E. Dane, F. Drees*, and *P. Konrad*, German Patent Application (Apr. 27th, 1961), Farbenfabriken Bayer.

[42] *L. Birkofer* and *A. Ritter*, Angew. Chem. *68*, 461 (1956); Liebigs Ann. Chem. *612*, 22 (1958).

[43] *K. Rühlmann*, J. prakt. Chem. *281*, 86 (1959).

[44] *K. Rühlmann*, J. prakt. Chem. *281*, 315 (1959).

[45] *K. Rühlmann* and *G. Michael*, Z. Naturforsch. *15b*, 811 (1960); *K. Rühlmann*, Chem. Ber. *94*, 1876 (1961).

[46] *L. Birkofer* and *A. Ritter*, Chem. Ber. *93*, 424 (1960).

[47] *T. Wieland* and *B. Heinke*, Liebigs Ann. Chem. *599*, 70 (1956).

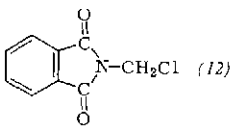
[48] *G. W. Anderson* and *R. Paul*, J. Amer. chem. Soc. *80*, 4423 (1958).

[49] *L. Birkofer, W. Konkel*, and *A. Ritter*, Angew. Chem. *71*, 701 (1959); Chem. Ber. *94*, 1263 (1961).

[50] *F. A. Henglein* and *W. Knoch*, Makromolekulare Chem. *28*, 10 (1958).

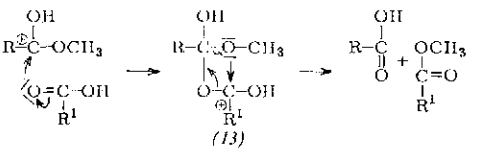
cillin V [51], may be split off under particularly mild conditions, *e.g.* with *p*-toluenesulfonic acid in boiling benzene or with trifluoroacetic acid at room temperature. Esterification of amino acids with t-butanol in the usual manner is not successful. *N*-Acylamino esters are obtained by alkylating with t-butyl acetate using an acid catalyst, preferably perchloric acid [52], or with isobutene in the presence of a small amount of conc. sulfuric acid [53]. These routes may also be used for esterifying free amino acids, when, in view of salt formation, more perchloric acid [54] or sulfuric acid [55] is needed. In these reactions the t-butyl cation probably acts as an alkylating agent. A special advantage of the t-butyl esters is their stability towards not too strong bases. For example, the free esters may be distilled without formation of diketopiperazine.

Similar lability to acids is shown by *p*-methoxybenzyl esters [15]; these may be obtained, for example, from carbobenzoxyamino acids and anisyl alcohol by eliminating water with dicyclohexylcarbodiimide. Another residue easily removed by acids is the phthalimidomethyl group proposed by *Nefkens* [56]. This is introduced by treating anions of *N*-acylamino acids with phthalimidomethyl chloride *(12)*. It may also be removed with


(12)

hydrazine. The contrary effect, resistance to even strong acids, is achieved by *p*-nitro-substitution of the benzyl residue. The *p*-nitrobenzyl esters of amino acids and peptides are substantially more stable towards HBr in glacial acetic acid than the benzyl esters [57]. *p*-Nitrobenzyl esters have been made by the action of *p*-nitrobenzyl bromide on amino acids in the presence of base [57,58], followed by removal of the group protecting the nitrogen. The free esters are now more readily obtainable by refluxing the free amino acids with *p*-nitrobenzyl alcohol and benzenesulfonic acid in carbon tetrachloride, leading the condensate over silica gel to dry it [59].

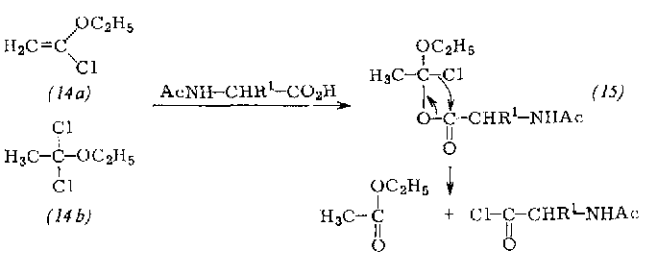
Methyl esters, which have already played a large part in peptide chemistry, are made efficiently and conveniently by treating the free amino acids with a solution of thionyl chloride in methanol at room temperature [60,61]. The laborious and not always fully satisfactory use of HCl is thus unnecessary. In order to esterify acylated amino acids, catalytic quantities of Lewis acids can be used according to *Taschner*. Sulfuryl chloride has proved best for making the methyl [62] and benzyl [63] esters. *N*-Acylamino acids can also be alkylated with methyl or ethyl formate or acetate in the presence of sulfuric acid [64]. This alkylation must proceed differently to the t-butylation mentioned above [52], perhaps via a protonated adduct *(13)* and intramolecular *O*-alkyl transfer.


(13)

Methods of Coupling

Use of Chlorides

The classical methods of coupling using the chlorides of protected amino acids keep recurring today in several variations. The chlorides are produced directly within the reaction mixture and react at once with the amino components. *Heslinga* and *Arens* [65] found that on heating acylamino acids or peptides with amino ester hydrochlorides and α-chlorovinyl ethyl ether *(14a)* or α,α-dichloroethyl ethyl ether *(14b)*, good yields of


(14a) *(14b)* *(15)*

peptides are obtained. It is assumed that retacion of *(14a)* or *(14b)* with the acylated amino acid leads via an unstable intermediate *(15)* to the acid chloride, which at once reacts further with the basic reactant. A more readily available compound, *viz.* dichloromethyl methyl ether gives the same results, according to *Rieche* [66]. Tosyl- and phthalylamino acids also react with excess reagent to give the acid chlorides, a method which is of preparative value; under these conditions, carbo-

[51] *J. C. Sheehan* and *K. R. Henery-Logan*, J. Amer. chem. Soc. *79*, 1263 (1957).

[52] *E. Taschner, B. Liberek, Cz. Wasielewski*, and *J. F. Biernat*, Angew. Chem. *71*, 743 (1959); *E. Taschner, C. Wasielewski*, and *J. F. Biernat*, Liebigs Ann. Chem. *646*, 119 (1961).

[53] *G. W. Anderson* and *F. M. Callahan*, J. Amer. chem. Soc. *82*, 3359 (1960).

[54] *E. Taschner, A. Chimiak, B. Bator*, and *T. Sokolowska*, Liebigs Ann. Chem. *646*, 134 (1961).

[55] *R. W. Roeske*, Chem. Industrie 1121 (1959).

[56] *G. H. L. Nefkens*, Nature (London) *193*, 974 (1962).

[57] *R. Schwyzer* and *P. Sieber*, Helv. chim. Acta *42*, 972 (1959).

[58] *H. Schwarz* and *K. Arakawa*, J. Amer. chem. Soc. *81*, 5691 (1959).

[59] *J. E. Shields, W. H. McGregor*, and *F. H. Carpenter*, J. org. Chemistry *26*, 1491 (1961).

[60] *M. Brenner* and *W. Huber*, Helv. chim. Acta *36*, 1109 (1953).

[61] *R. A. Boissonnas, St. Guttmann, P.-A. Jaquenoud*, and *J.-P. Waller*, Helv. chim. Acta *38*, 1491 (1955).

[62] E. *Taschner* and *C. Wasielewski*, Liebigs Ann. Chem. *640*, 136 (1961).

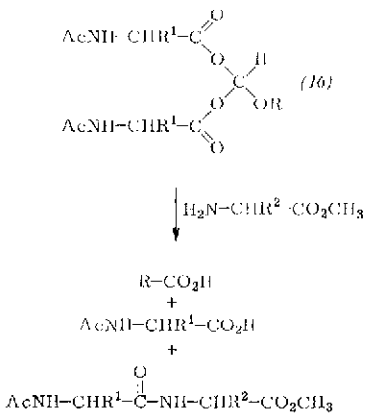
[63] *E. Taschner* and *C. Wasielewski*, Liebigs Ann. Chem. *640*, 139 (1961).

[64] *E. Taschner* and *C. Wasielewski*, Liebigs Ann. Chem. *640*, 142 (1961).

[65] *L. Heslinga* and *J. F. Arens*, Recueil Trav. chim. Pays-Bas *76*, 982 (1957).

[66] *A. Rieche* and *H. Gross*, Chem. Ber. *92*, 83 (1959).

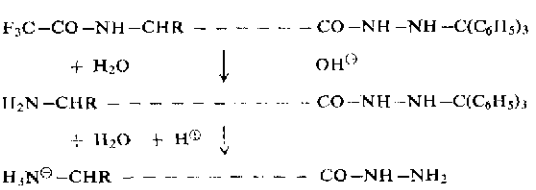
benzoxyamino acids are converted into *N*-carbamic anhydrides [67]. Mixed anhydrides *(16)* of acylamino acids and orthoformates can be isolated from the reaction between two moles of amino acid and one mole of dichloromethyl alkyl ether in a medium which binds HCl. In the reaction with amino esters, only one of the aminoacyl residues reacts to form a peptide bond.



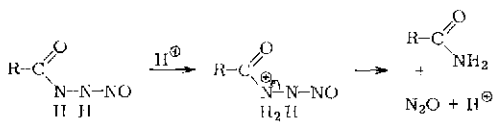
The reaction product from dimethylformamide and phosgene, *viz.* the chloride of *N,N*-dimethyliminoformyl chloride $[(CH_3)_2N{-}CH\ Cl]Cl$ [68], can also serve as a chlorinating agent for acylamino acids [69]. With this reagent, peptide bonds may be formed at 0 °C between acylamino acids and amino or peptide esters.

Use of Hydrazides and Azides

The use of azides for coupling according to *Curtius* has emerged in the course of recent years as the only method in which no racemization of the activated peptide components takes place. Several authors have therefore concerned themselves with the development of this procedure. One particular aim was to avoid the difficult hydrazinolysis of many long-chain peptide esters. Carbobenzoxyhydrazides had been recommended earlier for this purpose [70]; tritylhydrazine has now been suggested for introducing the azide [71]. Starting from the hydrazine derivative and a trifluoroacetylamino acid, treatment with dicyclohexylcarbodiimide or carbonyldiimidazole yields the tritylhydrazide of the trifluoroacetylamino acid – or of the trifluoroacetylpeptide; the trifluoroacetyl group is then split off with alkali.

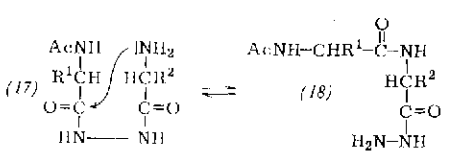


After further lengthening of the chain, the trityl residue can be split off with acid. The azide is then made with nitrous acid. The use of t-butyloxycarbonylhydrazine in combination with the carbobenzoxy group, which can be removed by catalytic hydrogenation, to protect the amino-end has also been recommended [72]. Here, too, the coupling can be effected with dicyclohexylcarbodiimide [72], or by the anhydride method [73]. The formation of azides from hydrazides and nitrous acid is occasionally accompanied by a more or less extensive side-reaction, involving evolution of N_2O from



the primary *N*-nitrosohydrazide to form the amide. This side-reaction can be averted by using higher proton and nitrite concentrations, or by nitrosation in an organic solvent with esters of nitrous acid or with nitrosyl chloride [74].

Hydrazides of peptides which are slow to react may be formed very easily from thiophenyl esters [75]. Since the azide group can also be introduced by the mixed anhydride method [76,77], this process will perhaps also be of use in peptide chemistry. The principle of aminoacyl insertion has been recently extended by *Brenner* and coworkers [78] to hydrazine derivatives. *N,N'*-Diaminoacylhydrazines, in which one amino group is acylated *(17)*, undergo rearrangement in the presence of organic acids or bases to give peptide



hydrazides *(18)*. This is the inverse of the isomerization observed by *Kurtz* and *Niemann* [79] of hydrazides of acylamino acids into diacyl hydrazines. For aminoacylation, it is preferable to react the acylhydrazines with *N*-carboxyamino acid anhydrides in acetic acid. The peptide hydrazides can then be lengthened either by the methods outlined here or by the classical route via the azides, or oxidized with hypobromous acid to peptides with free carboxyl groups.

When oxidized with *N*-bromosuccinimide (NBS) in the presence of an amino acid or peptide ester, the hydra-

[67] *K. Poduska* and *H. Gross*, Chem. Ber. *94*, 527 (1961).

[68] *H. H. Bosshard, R. Mory, M. Schmid*, and *H. Zollinger*, Helv. chim. Acta *42*, 1653 (1959).

[69] *M. Zaoral* and *Z. Arnold*, Tetrahedron Letters No. *14*, 9 (1960).

[70] *K. Hofmann, A. Lindenmann, M. Z. Magee*, and *N. H. Khan*, J. Amer. chem. Soc. *74*, 470 (1952).

[71] *F. Weygand* and *W. Steglich*, Chem. Ber. *92*, 313 (1959).

[72] *R. Schwyzer*, Angew. Chem. *71*, 742 (1959); Chimia *14*, 366 (1960).

[73] *R. A. Boissonnas, S. Guttmann*, and *P. A. Jaquenoud*, Helv. chim. Acta *43*, 1349 (1960).

[74] *J. Honzl* and *J. Rudinger*, Collect. czechoslov. chem. Commun. *26*, 2333 (1961).

[75] *T. Wieland* and *B. Heinke*, Liebigs Ann. Chem. *615*, 184 (1958).

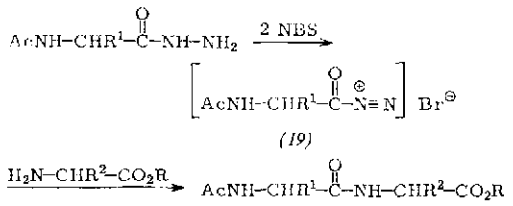
[76] *P. R. Bhandari*, Ph.D. thesis, Universität Mainz (1953).

[77] *J. Weinstock*, J. org. Chemistry *26*, 3511 (1961).

[78] *M. Brenner* and *W. Hofer*, Helv. chim. Acta *44*, 1794, 1798 (1961); *R. Weber, W. Hofer, W. Heer*, and *M. Brenner*, Helv. chim. Acta *44*, 2154 (1961).

[79] *A. N. Kurtz* and *C. Niemann*, J. Amer. chem. Soc. *83*, 3309 (1961).

zides of carbobenzoxyamino acids or peptides form peptides in very good yield and with negligible racemization [80]. The reaction may also be used for making polypeptides from tripeptide hydrazides. No details of the mechanism of the reaction, which perhaps proceeds via an acyldiazonium salt *(19)*, are yet known.

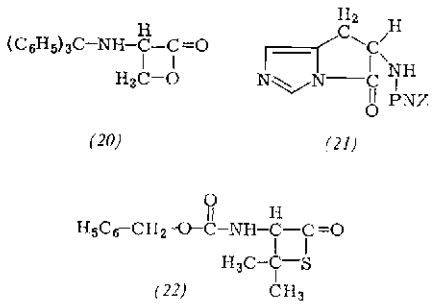


(19)

Use of Unsaturated Compounds

Compounds with double bonds which readily undergo addition reactions can add on acylamino acids, giving reactive intermediate products. If peptides are to be made, the intermediates are not isolated but are condensed in the reaction mixture with the basic components. To clarify the reaction mechanism of the activation of carboxyl groups by carbodiimides, experiments were made in the absence of the components to be coupled. On applying the customary method used with these reagents [81] to several carbobenzoxyamino or phthalylamino acids [82,83], symmetrical anhydrides were isolated: these are known to yield peptides with amino esters. It is thus not unlikely that such anhydrides are also formed as intermediates in peptide syntheses with dicyclohexylcarbodiimide [84].

During peptide synthesis, *N*-(3-Dimethylaminopropyl)-*N'*-t-butylcarbodiimide [85] takes up water to give a urea which is soluble in dilute acids and thus can be removed readily. This also holds for other basic carbodiimides, *Sheehan* [86] having shown that it applies particularly for *N*-ethyl-*N'*-3-(dimethylaminopropyl)-carbodiimide. Carbodiimides are obtained from the ureas by dehydration with tosyl chloride and triethylamine. They may be methylated in ether to give the equally useful quaternary methylammonium salts. The dehydrating action of carbodiimides was used by *Sheehan* [87,88] for the synthesis of some amino acid derivatives that are themselves reactive. *N*-Tritylserine gives a β-lactone *(20)* which reacts with the methyl ester of alanine without racemization to yield the dipeptide ester derivative. *N*-(*p*-Nitrobenzoxycarbonyl)-histidine gives the lactam *(21)*, which acts as an acylating agent; the β-thiolactam from *N*-carbobenzoxy-3,3-dimethylcysteine *(22)* has the same effect.

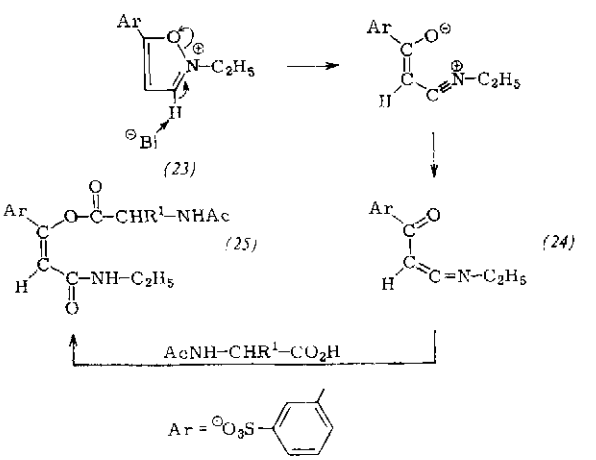


(20) *(21)*

(22)

Cyanamide, which perhaps reacts in its tautomeric form as carbodiimide, and also unsymmetrically dialkylated cyanamides bring about peptide synthesis from carbobenzoxyamino acids and amino esters on heating at 100 °C without solvent for two hours, yields of 60 to 70 % being obtained [89]. In the latter case too, acylated isourea derivatives may be the actual carriers of the acyl group.

Special interest has been attracted by the introduction of a new reagent for making peptides by *Woodward* and coworkers [90]. Yields of 73 to 93 %, with negligible racemization, are quoted for 16 examples of syntheses of di- and tripeptides using *N*-ethyl-5-phenylisoxazolium-3'-sulfonate *(23)*. In the mechanism suggested for this interesting reaction, the hydrogen next to the positive nitrogen is supposed to be lost as a proton to a base, whereupon an oxoketenimine *(24)* is formed by opening of the ring [91]. The protected amino acid adds onto this at once, and the actual reactant, the *O*-aminoacylenol *(25)*, is formed by migration of the acyl group.



(23) *(25)* *(24)*

Use of Activated Esters

One of the first types of compounds of this nature, *viz.* a cyanomethyl ester [92], has also been used for a tri-

[80] *Y. Wolman, P. M. Gallop,* and *A. Patchornik,* J. Amer. chem. Soc. *83,* 1263 (1961).

[81] *F. Zetzsche* and *H. Lindlar,* Ber. dtsch. chem. Ges. *71,* 2095 (1938); *F. Zetzsche* and *A. Fredrick, ibid. 72,* 363 (1939).

[82] *H. Schüssler* and *H. Zahn,* Chem. Ber. *95,* 1076 (1962).

[83] *I. Muramatsu* and *A. Hagitani,* J. chem. Soc. Japan *80,* 1497 (1959); Chem. Abstr. *55,* 6394 (1961); *I. Muramatsu,* J. chem. Soc. Japan *82,* 83 (1961); Chem. Abstr. *56,* 10273 (1962).

[84] *J. C. Sheehan* and *G. P. Hess,* J. Amer. chem. Soc. *77,* 1067 (1955).

[85] German Pat. 1070639 (Dec. 1959), Farbenfabriken Bayer, Inventors: *H. B. König* and *F. Moosmüller*; Chem. Abstr. *55,* 11324 (1961).

[86] *J. C. Sheehan, P. A. Cruickshank,* and *G. L. Boshart,* J. org. Chemistry *26,* 2525 (1961).

[87] *J. C. Sheehan,* Ann. N. Y. Acad. Sci. *88,* 665 (1960); Chem. Abstr. *55,* 25779 (1961).

[88] *J. C. Sheehan, K. Hasspacher,* and *Y. L. Yeh,* J. Amer. chem. Soc. *81,* 6086 (1959).

[89] *G. Losse* and *H. Weddige,* Angew. Chem. *72,* 323 (1960); Liebigs Ann. Chem. *636,* 144 (1960).

[90] *R. B. Woodward, R. A. Olofson,* and *H. Mayer,* J. Amer. chem. Soc. *83,* 1010 (1961).

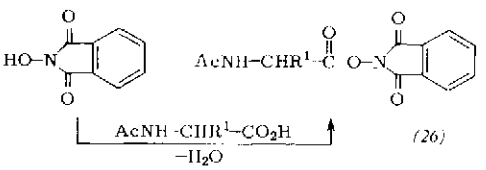
[91] *R. B. Woodward* and *R. A. Olofson,* J. Amer. chem. Soc. *83,* 1007 (1961).

[92] *R. Schwyzer, M. Feurer, B. Iselin,* and *H. Kägi,* Helv. chim. Acta *38,* 80 (1955).

peptide synthesis without isolation of the intermediate products [93]. In addition, it was found that treatment with HBr in glacial acetic acid hydrates the nitrile carbon and thus gives rise to aminocarbonylmethyl esters $H_2N\ CHRCOOCH_2\ CONH_2$, which have no acylating activity. In the paper cited, *p*-nitrophenyl-dipeptide esters are also used as activated dipeptides. For example, carbobenzoxyamino acids are first treated with aminoacyl-*p*-nitrophenols by means of the anhydride method or dicyclohexylcarbodiimide, forming the *p*-nitrophenyl esters of the carbobenzoxy-dipeptides, which react further without isolation with another amino ester.

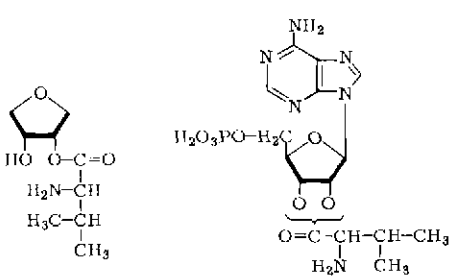
The *p*-nitrophenyl esters may be obtained from acylamino acids and the corresponding sulfite $OS(OAr)_2$ or phosphite $P(OAr)_3$ [94] as well as from their components using dicyclohexylcarbodiimide [95–97]. Heating of the acids with di-*p*-nitrophenyl carbonate $OC(OAr)_2$ [98] is also successful. Numerous other phenyl esters have also been made by the sulfite and phosphite methods [94]. The *p*-methylsulfonylphenyl esters have recently been used [99] on account of the resistance of this group later on, when the *N*-protecting group has to be split off by catalytic hydrogenation. Phenyl esters of acylated amino acids [100], *e.g.* the α-phenyl ester of carbobenzoxyglutamic acid, have proved suitable for the synthesis of α-glutamyl peptides [101], although they are much less active. 2,4,6-Trichlorophenyl esters of several *N*-protected amino acids have proved useful acylating agents for the synthesis of dipeptides at room temperature [102].

Although all peptide syntheses with activated amino esters had previously been carried out in presence of bases, *Weygand* and *Steglich* [103] found that activated esters, particularly the thiophenyl esters of carbobenzoxyamino acids, reacted with free amino acids to form peptides when heated in glacial acetic acid. The zwitterionic forms of the amino acids seem to be partly abolished by the action of the solvent on both polar groups. The time necessary for reaction and the yield are strongly dependent upon steric factors. Carbobenzoxyglycylglycine is formed in 60 minutes in 92 % yield, but the reaction of the thiophenyl ester of carbobenzoxyleucine with alanine yields only 43 % peptide in 10.5 hours. The nitrogen of the amino acid component is acylated in a secondary reaction. Steric hindrance affects the thiophenyl esters of phthalylamino acids most unfavorably [28]. To reduce steric hindrance as much as possible, activated vinyl esters have been made from some acylamino acids by transvinylation with vinyl acetate and palladium chloride [104]. The acetaldehyde produced by the condensation with amino esters is taken up by the solvent, cyanoacetic ester. Some dipeptide esters are formed in this way in more than 80 % yield. A new activated ester introduced into peptide chemistry by *Nefkens* and *Tesser* [105] is the hydroxyphthalimide "ester" *(26)* of carbobenzoxyamino acids. This ester is obtained in moderate to good yields by the action of dicyclohexylcarbodiimide on carbobenzoxyamino acids and *N*-hydroxyphthalimide, which is made from hydroxylamine and the phthalylating agent [27] *N*-ethoxycarbonylphthalimide *(7)*.



(26)

The activated amino acids that occur in nature, *i.e.* 2′- or 3′-amino esters containing terminal adenosine groups from specific, soluble ribonucleic acids [106], have hitherto only been prepared enzymatically. In order to understand the ease of aminolysis of these esters, *Zachau* and *Karau* [107] and *Wieland, Merz*, and *Pfleiderer* [108] synthetized amino esters of several cyclic glycols and compared their rates of reaction with hydroxylamine with that of amino esters of some nucleotides. It turned out that either a free adjacent hydroxyl group or an oxygen atom in the ring have an accelerating effect. The valine ester of *cis*-3,4-dihydroxytetrahydrofuran *(27)*, the most active compound, still reacted significantly slower with hydroxylamine than 2′-(or 3′-)valyl-adenosine-5-phosphoric acid *(28)*; hence it must be



(27) *(28)*

concluded that the purine nitrogen, and perhaps also the phosphoric acid, have an additional effect. This effect is shown in the comparison of the rates of cleavage

[93] *M. Goodman* and *K. C. Stueben*, J. Amer. chem. Soc. *81*, 3980 (1959).

[94] *B. Iselin, W. Rittel, P. Sieber*, and *R. Schwyzer*, Helv. chim. Acta *40*, 373 (1957).

[95] *M. Rothe* and *F.-W. Kunitz*, Angew. Chem. *68*, 414 (1956); Liebigs Ann. Chem. *609*, 88 (1957).

[96] *D. F. Elliot* and *D. W. Russel*, Biochem. J. *66*, 49 P (1957).

[97] *M. Bodánszky* and *V. Du Vigneaud*, J. Amer. chem. Soc. *81*, 5688 (1959).

[98] *T. Wieland, B. Heinke, K. Vogeler*, and *H. Morimoto*, Liebigs Ann. Chem. *655*, 189 (1962).

[99] *R. Schwyzer* and *P. Sieber*, Helv. chim. Acta *41*, 2190 (1958).

[100] *T. Wieland* and *W. Schäfer*, Angew. Chem. *63*, 146 (1951); *T. Wieland* and *F. Jaenicke*, Liebigs Ann. *599*, 125 (1956); see [103].

[101] *E. Klieger* and *H. Gibian*, Liebigs Ann. Chem. *655*, 195 (1962).

[102] *G. Kupryszewski*, Roczniki Chem. *35*, 595 (1961); Chem. Abstr. *55*, 27121 (1961).

[103] *F. Weygand* and *W. Steglich*, Chem. Ber. *93*, 2983 (1960).

[104] *F. Weygand* and *W. Steglich*, Angew. Chem. *73*, 757 (1961).

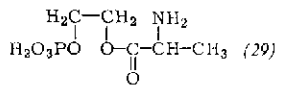
[105] *G. H. L. Nefkens* and *G. J. Tesser*, J. Amer. chem. Soc. *83*, 1263 (1961).

[106] *H. G. Zachau, G. Acs*, and *F. Lipmann*, Proc. nat. Acad. Sci. U.S.A. *44*, 885 (1958).

[107] *H. G. Zachau*, Chem. Ber. *93*, 1822 (1960); *H. G. Zachau* and *W. Karau*, Chem. Ber. *93*, 1830 (1960).

[108] *T. Wieland, H. Merz*, and *G. Pfleiderer*, Chem. Ber. *93*, 1816 (1961).

with hydroxylamine of 1-DL-alanyl-2-phosphorylglycol *(29)*, alanylglycol, and the methyl ester of alanine [109]. In the teichoic acids *(30)* of bacterial cell walls, which are D-alanyl esters of poly(glycerol phosphate) or poly(ribityl-1,5-diphosphate), reactivities of the esterified alanine residues were observed which corresponded approximately to that of the activated amino acids of the cell [110].



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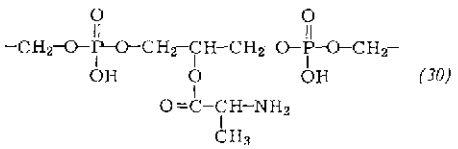
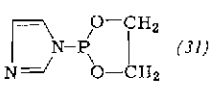


(30)

Use of Phosphorus Derivatives

Diphenylphosphoryl chloride has been added [111] to the numerous phosphorus derivatives proposed as components for activating amino acids.

Phosphorus pentoxide has been introduced as a reagent for peptide synthesis by *Schramm* and *Wissmann*. The method was tried out on several peptides: protected amino acids and amino esters were dissolved in diethyl phosphite and heated with tributylamine and P_2O_5 on a steam bath [112]. This process gives racemic tripeptides but is particularly suitable for manufacturing large quantities of dipeptides, as very concentrated solutions can be used. It is supposed that ethyl polyphosphates formed from P_2O_5 and diethyl phosphite are the actual condensing agents. Derivatives of phosphorous acid recommended as being useful for peptide bonding include, in addition to the tetraethyl pyrophosphite customary before, bis-*o*-phenylene pyrophosphite – prepared from pyrocatechol and phosphorus trichloride [113] – and diethylethylene pyrophosphite [18]. In peptide syntheses with these reagents, an equivalent quantity of imidazole has an accelerating effect. *Anderson* [114] has therefore synthetized ethylene *P*-imidazolyl phosphonite *(31)* and used it in place of the reaction mixture as a

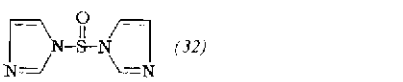


(31)

condensing agent. He obtained yields about 10 % higher than those obtained by the pyrophosphite method without imidazole.

Nothing has been reported about the mode of action of imidazole (see above), yet it may be supposed that an imidazolide of the amino acid is an intermediate. After these energy-rich compounds [115] – which can be coupled without isolation according to *Paul* and *Anderson* [48] – became readily accessible by the smooth reaction of *N,N'*-carbonyldiimidazole [116] with protected peptides and amino acids; the discoverers of this procedure applied themselves to working out the optimum conditions [117]. The ethyl ester of carbobenzoxyglycyl-L-phenylalanylglycine, which is – as mentioned later – the most frequently used test compound for racemization studies, was obtained in 90 % yield, along with 5 % of the DL-tripeptide. During the formation of the acylimidazole, an excess of carbonyldiimidazole was avoided, and water was excluded. The coupling components, *e.g.* salts of amino acids, may then be added in the presence of water, but use of esters without water is recommended.

Staab and *Wendel* [118,119] later described thionyldiimidazole *(32)*, which is readily obtained from thionyl chloride and four equivalents of imidazole in tetrahydrofuran at room temperature and can also be used without isolation for peptide syntheses in one-step reactions [120]. Compound *(32)* reacts at 0 °C with carbobenzoxyalanine to give the imidazolide *(33)*, even



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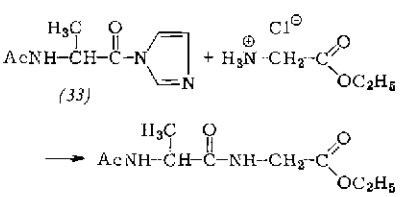


(33)

when the ester component – protected as its hydrochloride – is present. Peptide coupling is initiated by addition of triethylamine. The yields are so far around 75 %, but can probably be raised. A phosphoryldiimidazole, *viz.* the diimidazolide of phenylphosphoric acid, is also capable of transfering an imidazole residue to an acylamino acid to form its imidazolide, which can then be treated with alanine to give a peptide [121].

Free imidazole is known to be able to catalyse hydrolysis of reactive esters [122]. This process, which is thought to entail intermediate formation of an *N*-acylimidazole [123], may also be used to activate alkyl

[109] *Z. A. Shabarowa, N. A. Hughes*, and *J. Baddiley*, Biochem. J. *83*, 216 (1962).

[110] *A. R. Archibald, J. J. Armstrong, J. Baddiley*, and *J. B. Hay*, Nature (London) *191*, 570 (1961).

[111] *A. Cosmatos, J. Photaki*, and *L. Zervas*, Chem. Ber. *94*, 2644 (1961).

[112] *B. F. Erlanger* and *N. Kokowsky*, J. org. Chemistry *26*, 2534 (1961).

[113] *P. C. Crafts, J. H. H. Markes*, and *H. N. Rydon*, J. chem. Soc. (London) *1959*, 3610.

[114] *G. W. Anderson*, Ann. N. Y. Acad. Sci. *88*, 676 (1960).

[115] *T. Wieland* and *G. Schneider*, Liebigs Ann. Chem. *580*, 159 (1953).

[116] *H. A. Staab*, Liebigs Ann. Chem. *609*, 75 (1957).

[117] *R. Paul* and *G. W. Anderson*, J. Amer. chem. Soc. *82*, 4596 (1960).

[118] *H. A. Staab* and *K. Wendel*, Chem. Ber. *93*, 2902 (1960).

[119] *H. A. Staab*, Angew. Chem. internat. Edit. *1*, 351 (1962).

[120] *T. Wieland* and *K. Vogeler*, Angew. Chem. *73*, 435 (1961).

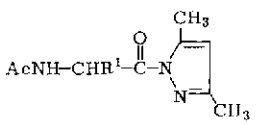
[121] *F. Cramer* and *H. Schaller*, Chem. Ber. *94*, 1634 (1961).

[122] See *M. L. Bender*, Chem. Reviews *60*, 53 (1960).

[123] *M. L. Bender* and *B. W. Turnquest*, J. Amer. chem. Soc. *79*, 1656 (1957).

esters of acylamino acids [124]. On stirring the methyl ester of carbobenzoxyalanine for several hours with the sodium salt of glycine in liquid imidazole at 80 °C, over 60 % of the carbobenzoxy-dipeptide is obtained; with the more soluble tetraethylammonium salt the yield is over 70 %; without imidazole, no coupling takes place. By using the t-butyl ester of glycine under these conditions, 75–80 % of the carbobenzoxy-dipeptide ester may even be attained. In this connection, we found that the phthalyl residue is rapidly split off on heating with imidazole in the presence of a little water.

3,5-Dimethylpyrazolides *(34)* of *N*-acylamino acids and peptides are significantly less reactive than the imidazolides [125]. They can be made from the acids and 3,5-dimethylpyrazole by the 'anhydride method' [126]. A further azole introduced into peptide chemistry as a coupling reagent is 1,2,4-triazole, which is applied in the form of *N,N'*-carbonyl-bis-1,2,4-triazole *(35)* [127].



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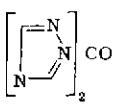


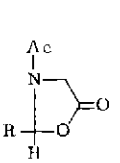
(35)

It is prepared in the same manner as carbonyldiimidazole; addition of one mole of pyridine to capture the acid formed in this reaction raises the yield. The compound, in which the positions of attachment of the carbonyl group are not known exactly, reacts more slowly in the activation step than the imidazole analogue, but faster in the coupling step. For example, the triazolides react rapidly with amino acids or peptide esters in dimethylformamide at room temperature, forming peptide bonds.

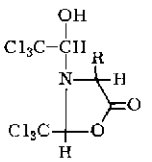
Sundry Methods

Oxazolidones. The procedure of *Micheel* and coworkers utilizing oxazolidones has also been further developed recently. It may be used with tosyl-L-glutamic acid [128] and other tosyl-L-amino acids [129] and gives dipeptides without racemization.

Acetic anhydride and thionyl chloride (in catalytic quantities) are now used to form the ring. Carbobenzoxyglycine has also yielded oxazolidones *(36)* with paraldehyde, benzaldehyde, or chloral by dehydration [130]. Chloral gives the best yield of oxazolidone. *Dane* and coworkers [131] found that this aldehyde reacts even with free amino acids to give 1,3-oxazolidine-5-one derivatives *(37)* in which the nitrogen bears the trichlorohydroxyethyl residue. These compounds react smoothly with amines at 20–40 °C and thus with glycine esters to give *N*-formyl-dipeptide esters.

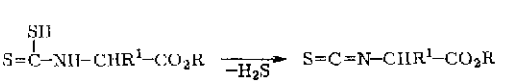


(36), R = CH_3, C_6H_5, CCl_3

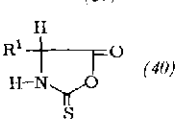


(37)

Carbonic Acid Derivatives. Mixed alkylcarbonic anhydrides still deserve consideration, although no novelty in the method has been forthcoming. Studies of theoretical interest have been made on the mechanism of decomposition of mixed carboxylic carbonic anhydrides (formation of ester and CO_2; disproportionation) using the mixed anhydride of benzoic and n-butylcarbonic acids as a model; the decomposition is supposed to be base-catalysed [132]. Mixed anhydrides may be obtained from carbobenzoxy-ε-aminocaproic acid by reaction with diethyl pyrocarbonate and used in the normal way for acylating the amino group of a second component [133]. With α-amino acids, however, such a synthesis is not possible [98]. Cyanuryl chloride reacts with acylated amino acids in the presence of a tertiary base at 0 °C to give an anhydride-like compound which gives a dipeptide on reaction with an amino ester. A dipeptide ester was formed in 77 % yield from carbobenzoxyalanine and glycine ester. On activation of a peptide, however, extensive racemization occurred [134]. The carbobenzoxy group can also be used for peptide bonding: on fusion with phthalylamino acids, *N*-carbobenzoxyaminoesters lose carbon dioxide and give dipeptide esters [98]. The mechanism here entails initial elimination of benzyl alcohol, leaving an isocyanato-fatty ester which condenses with acylamino acids in a familiar manner, carbon dioxide being evolved. α-Isothiocyanato-fatty esters *(38)* behave similarly, carbonyl sulfide being split off [89]. They are obtained from amino esters with carbon disulfide and alkali, the dithiocarbaminates *(39)* initially formed being treated with $HgCl_2$ to remove H_2S. Isothiocyanates are also formed from free amino acids with carbon disulfide, but cannot be isolated. They give polypeptides, probably via intramolecular thiocarbamic



(39) *(38)*



(40)

[124] *T. Wieland* and *K. Vogeler*, Angew. Chem. internat. Edit. *2*, 42 (1963).

[125] *W. Ried* and *A. Czack*, Liebigs Ann. Chem. *642*, 133 (1961).

[126] *W. Ried* and *K. Marquard*, Liebigs Ann. Chem. *642*, 141 (1961).

[127] *H. C. Beyermann* and *W. Maassen van den Brink*, Recueil. Trav. chim. Pays-Bas *80*, 1372 (1961).

[128] *F. Micheel* and *H. Haneke*, Chem. Ber. *92*, 309 (1959).

[129] *F. Micheel* and *H. Haneke*, Chem. Ber. *95*, 1009 (1962).

[130] *F. Micheel* and *W. Meckstroth*, Chem. Ber. *92*, 1675 (1959).

[131] *E. Dane*, *R. Heiss*, and *H. Schäfer*, Angew. Chem. *71*, 339 (1959); German Pat. 1079648 (Apr. 1960), Farbenfabriken Bayer; Chem. Abstr. *55*, 25784 (1961).

[132] *E. J. Longosz* and *D. S. Tarbell*, J. org. Chemistry *26*, 2161 (1961).

[133] *W. Thoma* and *H. Rinke*, Liebigs Ann. Chem. *624*, 30 (1959).

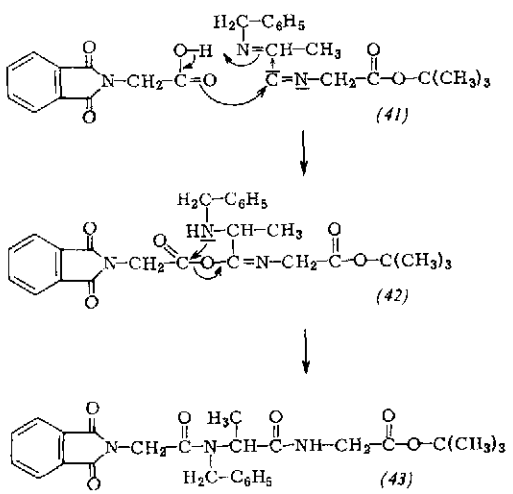
[134] *Th. Wieland* and *P. Duesberg*, unpublished.

anhydrides *(40)*. *N*-(Phenylthiocarbonyl)-amino acids ($H_5C_6S-CO-NH-CHR-CO_2H$) and -peptides [135] as well as *N*-(phenyloxycarbonyl)- and *N*-(*o*-nitrophenyloxycarbonyl)-amino acid derivatives [136] also exhibit this readiness to polymerize.

Other Mixed Anhydrides. Actually all activated derivatives of acylamino acids may be considered in principle as mixed anhydrides. A recent review [6] of methods of peptide coupling is written from this point of view, but the finer distinctions will be retained here.

Diphenyl ketene reacts very rapidly with acylated amino acids at −15 °C to form mixed anhydrides of diphenylacetic acid. Owing to steric hindrance, only the acylamino portion is able to react with amino esters to form peptides [137]. Benzenesulfonic acid can be introduced easily as an anhydride component by treating acylamino acids with benzenesulfonyl chloride. Such anhydrides have also been used for peptide syntheses [138], but they seem to offer no particular advantage, as has been confirmed recently using toluenesulfonic acid as one anhydride component [139]. The use of toluenesulfonyl chloride for esterification with slow-reacting alcohols, in which a mixed anhydride is formed as an intermediate, has been recommended since 1955 [140]. Methyl sulfonyl chloride has also been used to make a peptide bond [141].

Passerini Reaction. Recently, *Ugi* [142] has reported a remarkable application of the Passerini reaction in the presence of an amine, two peptide links being formed simultaneously. A striking example is the reaction of t-butyl isocyanoacetate *(41)*, which is obtained from the t-butyl ester of *N*-formylglycine by dehydration with phosgene and triethylamine, by analogy to the isonitrile synthesis from formamide with phosphorus oxychloride in pyridine [143]. The ester *(41)* reacts at room temperature within five hours in a multicentre process with phthalylglycine, benzylamine, and acetaldehyde (a Schiff-base) via an *O*-acylpeptide *(42)* to form the t-butyl ester of phthalylglycyl-(*N*-benzyl-DL-alanyl)glycine *(43)* in 73 % yield. Although the middle amino acid becomes racemic in the process, this elegant reaction may attain importance in peptide chemistry. In the absence of an amine, the analogous reaction gives rise to a depsipeptide [144].

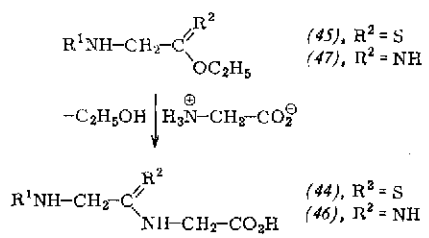


(41)

(42)

(43)

Degenerate Peptides. The class of compounds known as depsipeptides, also called peptolides [145], which includes several interesting natural products, has been reviewed recently by *Schemjakin* [146]. In addition to the principles of synthesis described therein, which *Schemjakin* has lately followed for the synthesis of optically active depsipeptides [147], a special route has been described by which a glycolic acid residue may be introduced specifically into an ester bond by way of diazoacetylamino acid derivatives [148, 149]. *Ried* and coworkers have studied the synthesis of other peptide-like compounds. The so-called *endo*-thiopeptides *(44)* were obtained by condensation of acylaminothionic esters *(45)* with salts of amino acids [150]; imidopeptides *(46)* are formed in a similar manner [151] from iminoesters *(47)*.



(45), $R^2 = S$
(47), $R^2 = NH$

(44), $R^2 = S$
(46), $R^2 = NH$

Syntheses of Cyclic Peptides

Attempts to prepare cyclic peptides with definite structures have been the aim of one branch of peptide chemistry. Systematic studies on the effect of dilution, which is known to be important in this field, have been made by *Rothe* and coworkers [152], albeit on a "degenerate" model. Cyclization of ε-aminocaproyl-ε-aminocaproyl chloride, which was set free from its hydrochloride by triethylamine in dimethylformamide, gave the yields shown in Table 1 after two hours' reaction. The yields depend upon the dilution.

[135] *J. Noguchi* and *T. Hayakawa*, J. Amer. chem. Soc. *76*, 2846 (1954).

[136] *Y. Ishizuka*, Nippon Kagaku Zasshi 77, 1426 (1956); Chem. Abstr. *53*, 5149 (1959).

[137] *G. Losse* and *E. Demuth*, Chem. Ber. *94*, 1762 (1961).

[138] *E. Taschner*, Collect. czechoslov. chem. Commun. *24*, 26 (1959); see also Chem. Abstr. *52*, 16236 (1958).

[139] *D. Theodoropoulos* and *J. Gazapoulos*, J. org. Chemistry 27, 2091 (1962).

[140] *J. H. Brewster* and *C. J. Ciotti*, J. Amer. chem. Soc. *77*, 6214 (1955).

[141] *F. C. McKay*, cited by *N. F. Albertson* [6].

[142] *I. Ugi*, Angew. Chem. internat. Edit. *1*, 8 (1962).

[143] *I. Ugi* and *R. Meyr*, Chem. Ber. *93*, 239 (1960).

[144] *I. Ugi* and *U. Fetzer*, Angew. Chem. *73*, 621 (1961).

[145] *H. Gibian* and *K. Lübke*, Angew. Chem. *72*, 523 (1960).

[146] *M. M. Schemjakin*, Angew. Chem. *72*, 342 (1960).

[147] *M. M. Schemjakin* et al., Doklady Acad. Nauk SSSR *140*, 387 (1961); Chem. Abstr. *56*, 536 (1962).

[148] *R. Schwyzer* and *J. P. Carrión*, Helv. chim. Acta *43*, 2101 (1960).

[149] *H. Gibian* and *K. Lübke*, Liebigs Ann. Chem. *644*, 130 (1961).

[150] *W. Ried* and *W. von der Emden*, Angew. Chem. *72*, 268 (1960); Liebigs Ann. Chem. *642*, 128 (1961).

[151] *W. Ried*, *W. Stephan*, and *W. von der Emden*, Chem. Ber. *95*, 728 (1962).

[152] *M. Rothe*, *H. Brünig*, and *G. Eppert*, J. prakt. Chem. *280*, 323 (1959).

Table 1. Yields from cyclization of ε-aminocaproyl-ε-aminocaproyl chloride.

Concentration [mole/l]	Yield [%]
0.001	37
0.002	30
0.004	23
0.008	5

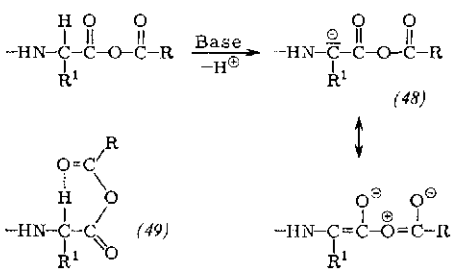
The concentration of 1 millimole per litre found here to be optimum is also used by most workers on similar problems. All the recognized coupling methods of peptide chemistry may in principle be used for cyclization. Of the activated esters, thiophenyl esters [75], cyanomethyl and *p*-nitrophenyl esters [153], carboxythiomethyl esters, and the *p*-methylsulfonylphenyl esters mentioned above [99] have been used. The protection of the amino group necessary during synthesis must be such that release is possible without attack on the activating group [99]. Ring closure without protection of the amino group and without special activation of the carboxyl group can be attained with dicyclohexylcarbodiimide [154] or ethoxyacetylene [155]. A more than one-hundred-fold excess of diimide permits formation of the four possible polymycins from the corresponding preformed decapeptides [156]. In the presence of bulky substituents (tosyl group) near to the point of linkage, ring closure is not successful [157]. In the dimeric cyclization of the *p*-nitrophenyl ester of DL-phenylalanylglycylglycine [99], the choice of a reaction partner is made in an interesting manner. *Schwyzer* and *Tun Kyi* [158] synthetized the authentic stereoisomeric cyclohexapeptides (L,L; D,D; D,L) by the azide method and found that dimerization gave rise exclusively to the *meso*-compound (D,L). Thus, only L-tripeptide molecules had combined with D-tripeptide molecules to form the hexapeptide ring.

Racemization during the Formation of Peptides [*]

Although free amino acids are very resistant to racemizing influences, a certain lability may be observed in a number of derivatives. Amino esters or *N*-acylamino acids are easily racemized by bases [159]. In principle, three possible types of racemization are to be distinguished:

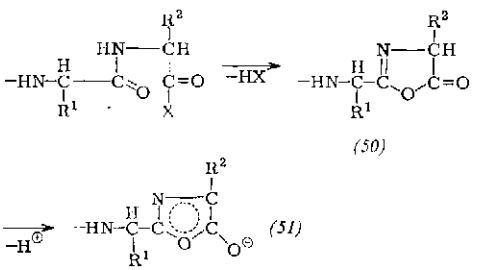
1. Racemization of amino acids in a peptide
2. Racemization of amino-acid anhydrides
3. Racemization of activated acylamino acids on account of ring formation.

Racemization in the peptide affects particularly amino acids bearing electron-attracting substituents (O, S) in the β-position, which effect a weakening of the binding of the α-hydrogen atom. An example from the recent literature is the observation by *McLaren* [9] that the ethyl ester of carbobenzoxyglycyl-L-(*S*-benzyl)cysteine racemizes extensively on saponification with alkali, although the acid remains optically active under these conditions. On treatment of the t-butyl ester of the same peptide with alkali, it is racemized completely, with liberation of the carboxyl group [114]. A serine peptide, the ethyl ester of carbobenzoxy-L-serylglycyl-L-alanine, rearranges on merely standing for several days at room temperature in aqueous triethylamine to give the diastereoisomeric DL-serine peptides until a state of equilibrium is reached [160]. The lability of amino acid anhydrides can be attributed to the electron-attracting property of the second acyl moiety *(48)* and probably also to the possibility of the loosening of the α-hydrogen atom by hydrogen bond formation *(49)* [159]. A base



may also be the actual isomerizing agent here. Although several *N*-acylimino acids, in which azlactone formation is out of the question, also become racemic as anhydrides [159], this form of racemization during peptide formation via anhydrides can nevertheless apparently be avoided if the anhydride stage is short and is formed at a low temperature. So far, no racemization of carbobenzoxyamino acids during activation has been observed. However, a sufficiently sensitive test has perhaps been lacking here.

Far more rapid racemization of activated amino acids seems to proceed during ring formation. *N*-Acylamino acids, including peptides, can be cyclized to azlactones *(50)* by loss of the elements of water. In such rings, loss of the proton is greatly facilitated because an aromatic



[153] *R. Schwyzer* and *P. Sieber*, Helv. chim. Acta *41*, 2186 (1958); *R. Schwyzer* and *B. Gorup*, Helv. chim. Acta *41*, 2199 (1958).

[154] *T. Wieland* and *K. W. Ohly*, Liebigs Ann. Chem. *605*, 179 (1957).

[155] *E. A. Morozova* and *S. M. Zhenodarova*, Zhur. Obshchei Khim. *31*, 45 (1961); Chem. Abstr. *55*, 27121 (1961).

[156] *K. Vogler*, *R. O. Studer*, *W. Lergier*, and *P. Lanz*, Helv. chim. Acta *43*, 1751 (1960); *R. O. Studer*, *K. Vogler*, and *W. Lergier*, Helv. chim. Acta *44*, 131 (1961); *K. Vogler*, *R. O. Studer*, *P. Lanz*, *W. Lergier*, and *E. Böhni*, Experientia *17*, 223 (1961).

[157] *R. O. Studer* and *K. Vogler*, Helv. chim. Acta *45*, 819 (1962).

[158] *R. Schwyzer* and *A. Tun-Kyi*, Helv. chim. Acta *49*, 859 (1962).

[*] Cf. *F. Weygand*, *A. Prox*, *L. Schmidhammer*, and *W. König*, Angew. Chem. internat. Edit. *2*, 183 (1963).

[159] *A. Neuberger*, Advances Protein Chem. *4*, 297 (1948).

[160] *E. Schnabel*, Hoppe-Seylers Z. physiol. Chem. *314*, 114 (1959).

system is then formed. Carbobenzoxyamino acids do not undergo ring closure, so that this protection of the amino group is not only advantageous on account of the case of removal of the protecting group. However, a greater or lesser degree of racemization has been observed so far even during the activation of dipeptides by almost every method (with the exception of the azide method).

Table 2. Racemization occuring during peptide syntheses.

Method of peptide coupling	Ref.	Racemization test or peptide synthetized	Result
Mixed anhydride (Carbonic acid derivatives) [a]	[164]	*Anderson* test [161] *Young* test [163]	2 % DL; 77 % L 46 % DL; 54 % L
Tetraethyl pyrophosphite	[165]	*Anderson* test *Young* test	0 % DL; 74 % L [b] 78 % L [b]
Dicyclohexylcarbodiimide	[84] [166]	*Anderson* test *Young* test *Anderson* test	87 % L [c] 74 % L [c] 7 % DL; 75 % L [c]
Carbonyldiimidazole	[48, 117]	*Anderson* test	0.5 % DL; 87 % L
Nitrophenyl ester	[168, 169]	Considerable racemization on esterification of dipeptides by the sulfite [168] and carbodiimide methods [169] [d]	
p-Nitrothiophenyl ester	[170]	Cbo-Gly-L-Ala/L-Phe-Gly-OH [e]	24 % DL; 56 % L
Sulfur trioxide	[162]	Cbo-Gly-L-Ala/L-Phe-Gly-OH [e]	0 % DL [f]
Ethoxyacetylene	[171]	*Anderson* test	0 % DL; 70 % L [g]
Phosphorazo method	[172] [173]	Cbo-Gly-L-Phe/L-Ala [e] *N*-acyl-*N*(ε)-Cbo-Lys	15 % DL; 80 % L retained full rotation on coupling [h]
Phosphorus pentoxide [i]	[174] [112]	Cbo-Gly-L-Leu/Gly-OC_2H_5 [e] *Anderson* test	63 % L 32 % DL; 32 % L
Isoxazolium method	[90]	*Anderson* test	2.2 % DL; 90 % L
N-Hydroxyphthalimide	[105]	[k]	not determined
Hydrazide oxidation	[80]	*Anderson* test	1.1 % DL; 63 % L
Phosgene/dimethylformamide	[69]		extensive racemization

[a] With chloroform as solvent, or on using higher temperatures during the formation of anhydride, the racemic fraction is significantly greater.

[b] This yield was obtained by the "standard" and the "amide" methods in the absence of quaternary salts. Considerable racemization takes place in the "anhydride" method, especially at higher temperatures.

[c] The discrepancy is explained by the fact that *Sheehan* and *Hess* [84] did not use the crystallization procedure which led to the detection of small quantities of racemate by *Anderson* and coworkers [161, 165, 166]. A further valuable contribution to this question is the synthesis of the tetrapeptide carbobenzoxy-nitro-L-arginyl-L-valyl-L-tyrosyl-L-isoleucine as its methyl ester [167] by all possible ways of coupling. If the carbobenzoxy-dipeptide or -tripeptide was coupled by way of the anhydride or with carbodiimide, significantly smaller yields were always obtained, the products being impure and not completely split by enzymes.

[d] The racemization seems to depend strongly upon the nature of the amino acid residue. Thus, carbobenzoxy-L-(*S*-benzyl)cysteinyl-L-tyrosine could be esterified smoothly and without racemization by the sulfite method, while carbobenzoxy-L-valyl-L-tyrosine gave only a small yield, the unreacted acid also undergoing considerable racemization [168].

[e] Cbo = carbobenzoxy.

[f] Note particularly that at somewhat higher pH values than that used here (6.5), the racemization is substantially greater.

[g] The presence of triethylammonium hydrochloride under otherwise equivalent conditions leads to a large fraction of racemic product.

[h] The discrepancy between the two experiments is not particularly serious, as the results of *Goldschmidt* and *Rosculet* [173] are only based on rotation measurements. It is doubtful here whether small quantities of racemate had been previously separated by crystallization, or do not show up in the results of the determination. Comparison of two tripeptides, one made from an acyl-dipeptide and an amino ester and the other from the acylamino acid and the dipeptide ester is not valid since in the critical cases glycine was involved in the coupling.

[i] The *Schramm* and *Wissmann* test [174] consists of the hydrolysis of the crystalline tripeptide followed by measurement of the rotation in comparison with that of an authentic amino acid mixture. *Erlanger* and *Kokowsky* [112] could not reduce racemization by variation of the coupling conditions.

[k] Performance of the "*Anderson* test" here [105] was inappropriate, as the tripeptide was made from the ethyl esters of carbobenzoxyglycine and of L-phenylalanylglycine, so that racemization is of course not possible.

[161] *G. W. Anderson* and *R. W. Young*, J. Amer. chem. Soc. *74*, 5307 (1952).

[162] *D. W. Clayton, J. A. Farrington, G. W. Kenner*, and *J. M. Turner*, J. chem. Soc. (London) *1957*, 1398.

[163] *N. A. Smart, G. T. Young*, and *M. W. Williams*, J. chem. Soc. (London), *1960*, 3902.

[163a] *M. W. Williams* and *G. T. Young*, J. chem. Soc. (London) *1963*, 881.

[164] *J. R. Vaughan, J.* Amer. chem. Soc. *74*, 7137 (1952).

[165] *G. W. Anderson, J. Blodinger*, and *A. D. Welcher*, J. Amer. chem. Soc. *74*, 5309 (1952).

[166] *G. W. Anderson* and *F. M. Callahan*, J. Amer. chem. Soc. *80*, 2902 (1958).

[167] *H. Schwarz* and *F. M. Bumpus*, J. Amer. chem. Soc. *81*, 890 (1959).

[168] *B. Iselin* and *R. Schwyzer*, Helv. chim. Acta *43*, 1760 (1960).

[169] *K. Lübke* and *E. Schröder*, Z. Naturforsch. *16b*, 765 (1961).

[170] *J. A. Farrington, P. J. Hextall, E. W. Kenner*, and *J. M. Turner*, J. chem. Soc. (London *1957*, 1407.

[171] *H. J. Pannemann, A. F. Marx*, and *J. F. Arens*, Recueil Trav. chim. Pays-Bas *78*, 487 (1959).

[172] *W. Grassmann, E. Wünsch*, and *A. Riedel*, Chem. Ber. *91*, 455 (1958).

[173] *St. Goldschmidt* and *G. Rosculet*, Chem. Ber. *93*, 2327 (1960).

[174] *G. Schramm* and *H. Wissmann*, Chem. Ber. *91*, 1073 (1958).

In order to determine the degree of racemization, the method worked out by *Anderson* [161] may be used. Carbobenzoxyglycyl-L-phenylalanine is coupled with the ethyl ester of glycine and the tripeptide formed is fractionally crystallized from a 2 % solution in alcohol. In this way, the DL-peptide precipitates first and can be recognized by its higher melting point. In a less commonly used test for racemization [162], use is made of the separability of carbobenzoxyglycyl-L-phenylalanyl-L-alanylglycine and carbobenzoxyglycyl-D-phenylalanyl-L-alanylglycine (synthetized from the dipeptides) by countercurrent distribution. A third procedure has been used by *Young* and coworkers [163] on several coupling methods under very different conditions. It entails the coupling of acetyl-L-leucine with the ethyl ester of glycine. The racemic and the optically pure dipeptides are not always obtained crystalline, however, so that the rotation must be measured both before and after hydrolysis, thus allowing only an approximate estimate of the degree of racemization. Recent investigations by the same author [163a] of peptides of *N*-benzoylleucine, which crystallize more readily, have not been considered in Table 2. The results obtained in tests for the racemization occuring during the methods of peptide bonding in general use are summarized in Table 2. The values given were determined under the conditions most favorable for retention of configuration.

It has already been indicated that the azide method is the only one in which the activated peptide component does not racemize. Table 2 shows that, apart from this procedure, there appears to be no ideal method of activation. The deficiency of the azide method lies in the hydrazinolysis of polypeptide esters, which sometimes proceeds unsatisfactorily. Here the catalytic acceleration with imidazole outlined above and the use of a somewhat more reactive ester may be of assistance. However, on the other hand, the dangers of racemization during very rapid coupling should not be exaggerated. Speedy execution of a peptide synthesis by the anhydride method using ethyl chloroformate at a low temperature can give good yields of pure L-peptides by activating dipeptides. A relatively safer, though more laborious procedure involves progressive attachment of carbobenzoxyamino acids which are known to racemize only with difficulty because of their lack of ability to form azlactones. A final possibility entails using peptides with glycine or proline at the carboxyl end. It should be noted that not all L-amino acids racemize to an equal extent, so that the choice of racemization resistant oligopeptides which can be coupled with others in a simple way may be further increased. Much systematic work is still to be done here. Enzymatic coupling [175] proceeds in the assurance that there is no racemization of the carboxyl end, but this will not be considered further here.

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German version: Angew. Chem. *75*, 539 (1963).

[175] See *H. Determann, O. Zipp,* and *T. Wieland,* Liebigs Ann. Chem. *651*, 172 (1962).

Base-Catalysed Reactions of Ketones with Hydrogen Sulfide [1]

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Monoketones react with hydrogen sulfide in the presence of basic catalysts to give geminal dithiols or thioketones. β-Diketones are converted into monothiodiketones. α-Diketones can be selectively reduced by hydrogen sulfide in the cold in the presence of secondary or tertiary amines to give hydroxy- or mono-ketones.

Base-catalysed additions of hydrogen sulfide onto carbonyl groups have been little investigated, although they form one of the fundamental reactions of organic chemistry. The reactions are also easily carried out technically, and the cheap intermediate products can be converted into heterocyclic sulfur compounds [2–4] in various ways. Some new results from our work will therefore be summarized in the following report.

The Base-Catalysed Reaction of Monoketones with Hydrogen Sulfide

If hydrogen sulfide is passed into a solution of a monoketone in the presence of a basic catalyst, *gem*-dithiols *(1)* or in special cases thioketones *(2)* are formed in varying yields.

We have recently described [2] this simple and most productive synthesis of the *gem*-dithiols *(1)*; hydrogen

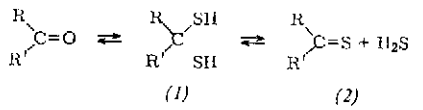
[1] XVIIth Communication on Sulfur Heterocycles. – XVIth Communication: *J. Franke* and *R. Mayer*, J. prakt. Chem., in the press.

[2] *J. Jentzsch, J. Fabian,* and *R. Mayer,* Chem. Ber. *95*, 1764 (1962).

[3] *B. Magnusson,* Acta chem. scand. *13*, 1715 (1959); *R. Mayer* and *J. Jentzsch,* Angew. Chem. internat. Edit. *1*, 217 (1962); *J. Jentzsch* and *R. Mayer,* J. prakt. Chem. (4) *18*, 211 (1962).

[4] *H. Barrera* and *R. E. Lyle,* J. org. Chemistry *27*, 641 (1962).

sulfide and ketones react in the presence of ammonia or amines at room temperature without the application of pressure. A little later, *Magnusson* [5] confirmed this result independently.



(1) *(2)*

a: R = R' = CH_3
b: R = CH_3; R' = C_2H_5
c: R = R' = C_2H_5
d: R = CH_3; R' = cyclohexyl
e: R/R' = $-(CH_2)_4-$
f: R/R' = $-(CH_2)_5-$
g: R/R' = $-(CH_2)_6-$
h: R = CH_3; R' = C_6H_5

Cairns and his collaborators [6] had already obtained compounds of type *(1)* in 1952 by allowing hydrogen sulfide to react with ketones or aldehydes at medium temperature and pressures of 35 to 8500 atm. Here addition of an amine did not lead to *(1)* as in our case, but to polysulfides; besides, it turned out that *gem*-dithiols are formed more readily from aldehydes than from ketones and that sterically hindered ketones react under these conditions only to a small extent. We discovered recently that such *gem*-dithiols *(1)* are very easily formed [7] and also arise by the action of H_2S in the cold on basic ketones [4] and ketimines [5]. Furthermore, *Djerassi* [8] and we ourselves [2] simultaneously succeeded in splitting enamines to give dithiols using hydrogen sulfide under mild conditions, whereas, according to *Nomura* and *Takeuchi* [9], thioketones *(2)* or products formed from them should be produced exclusively.

Compounds of type *(1)* are also accessible under acidic conditions [10,11], but these reactions will not be dealt with here.

The reaction conditions for the synthesis of *gem*-dithiols or thioketones depend on the ketone which is converted and can therefore be generalized only within limits. Temperatures of 0 to 20 °C have proved favorable; at higher temperatures, heterocyclic sulfur compounds occur as secondary products. Table 1 shows the optimum conditions under which *gem*-dithiols *(1)* or thioketones *(2)* are formed from ketones.

Benzophenone does not react; acetophenone first forms a yellow-orange oil, which decomposes on distillation to give thioacetophenone *(2h)* and other products such as ethylbenzene and styrene. On distillation of the product resulting from the reaction of H_2S and cyclohexyl methyl ketone, H_2S is eliminated and the unstable thioketone *(2d)* is formed. Compound *(2d)* absorbs at 236 and 508 mμ (in cyclohexane). Cycloheptanone is converted into cycloheptanethione *(2g)*, which shows characteristic maxima at 234 and 511 mμ (in cyclohexane).

Ammonia, primary, secondary and, in principle, also tertiary amines are suitable as catalysts (see Table 2), whereas alkali hydroxides and alkoxides are not. Tertiary amines appear to activate the ketone only when

Table 1. Reaction of monoketones with hydrogen sulfide to give *gem*-dithiols or thioketones. Temperature: 0 to 20 °C; reaction time: 7 h; solvent: 100 ml of dimethylformamide.

Ketone 0.5 mole	Amine 0.05 mole	Product	B.p. [°C/mm Hg]	Yield [%]	n_D^{25}
Dimethyl ketone	Morpholine	*(1a)*	57/100	34	1.5069
Ethyl methyl ketone	Morpholine	*(1b)* [*]	73/73	44	1.5072
Diethyl ketone	n-Butylamine	*(1c)*	72/30	31	1.5080
Cyclopentanone	Morpholine	*(1e)*	63/10	72	1.5469
Cyclohexanone	Morpholine	*(1f)*	84/12	83	1.5448
Cycloheptanone	n-Butylamine	*(2g)*	62/3	22	1.5563
Cyclohexyl methyl ketone	n-Butylamine	*(2d)*	62/2	20	1.5158
Acetophenone	n-Butylamine	*(2h)*	120/15	12	1.5609

[*] Dimethyl sulfoxide as solvent.

complex formation can occur, as has, for example, been demonstrated for cyclohexanone and trimethylamine at 0 °C [12]. Cyclohexanone is the only ketone of our series [13] which gives the corresponding dithiol *(1f)* with H_2S and triethylamine, albeit in only 11 % yield. These results can be seen from Table 2.

Table 2. Influence of the basic catalyst on the reaction of monoketones with hydrogen sulfide in dimethylformamide. Temperature: 0 to 20 °C; reaction time: 7 h.

Ketone (0.5 mole)	Catalyst (0.05 mole)	Product	Yield [%]
Ethyl methyl ketone	n-Butylamine	*(1b)*	39
	Morpholine	*(1b)*	29
	Triethylamine	—	—
	Ammonia	*(1b)*	31
Diethyl ketone	n-Butylamine	*(1c)*	31
	Morpholine	*(1c)*	3
	Triethylamine	—	—
	Ammonia	*(1c)*	23
Cyclohexyl methyl ketone	n-Butylamine	*(2d)*	20
	Morpholine	—	—
	Triethylamine	—	—
	Ammonia	*(2d)*	9
Cyclopentanone	Morpholine	*(1e)*	72
	Triethylamine	—	—
	Ammonia	*(1e)*	20
Cyclohexanone	Morpholine	*(1f)*	83
	Triethylamine	*(1f)*	11
	Ammonia	*(1f)*	25
Cycloheptanone	n-Butylamine	*(2g)*	22
	Morpholine	*(2g)*	14
	Triethylamine	—	—
	Ammonia	—	13
Acetophenone	n-Butylamine	*(2h)*	12
	Morpholine	—	—
	Triethylamine	—	—
	Ammonia	—	—
Benzophenone	n-Butylamine	—	—
	Morpholine	—	—
	Triethylamine	—	—
	Ammonia	—	—

Although some ketones react with hydrogen sulfide to give *gem*-dithiols without solvent having to be added, polar solvents in which H_2S is readily soluble are especially suitable. Such solvents are, *e.g.* dimethyl sulfoxide, dimethylformamide, and methanol. The influence of some solvents on the reaction of ethyl methyl ketone with hydrogen sulfide is shown in Table 3.

The mechanism of this base-catalysed synthesis of dithiols is still unclear. Nitrogenous bases certainly increase the nucleophilic properties of hydrogen sulfide, so that addition onto

[5] *B. Magnusson*, Acta chem. scand. *16*, 1536 (1962).

[6] *T. L. Cairns, G. L. Evans, A. W. Larchar*, and *B. C. McKusick*, J. Amer. chem. Soc. *74*, 3982 (1952).

[7] Cf. supposition of *E. Baumann*, Ber. dtsch. chem. Ges. *23*, 1869 (1890); *28*, 895 (1895).

[8] *C. Djerassi* and *B. Tursch*, J. org. Chemistry *27*, 1041 (1962).

[9] *Y. Nomura* and *Y. Takeuchi*, Bull. chem. Soc. Japan *33*, 1743 (1960).

[10] *R. Mayer* et al., unpublished results; cf. *G. A. Berchtold, B. E. Edwards, E. Campaigne*, and *M. Carmack*, J. Amer. chem. Soc. *81*, 3148 (1959); *E. Campaigne* and *B. E. Edwards*, J. org. Chemistry *27*, 3760 (1962).

[11] Moreover, under the conditions given by *D. C. Sen*, J. Indian chem. Soc. *13*, 268 (1936), enethiols are not formed exclusively, but also *gem*-dithiols; cf. [10].

[12] *O. H. Wheeler* and *E. M. Levy*, Canad. J. Chem. *37*, 1727 (1959).

[13] *R. Mayer* and *J. Fabian*, unpublished results.

Table 3. Influence of solvent on the yield of dithiol *(1b)* from ethyl methyl ketone (0.5 mole) and H_2S in the presence of morpholine (0.05 mole).

Solvent [100 ml]	Yield *(1b)* [%]
None	15
Dimethylformamide	29
Dimethyl sulfoxide	44
Methanol	11
Ether	7
Water	Trace
Glycol	Trace
Petroleum ether	Trace
Methylene chloride	Trace
Chloroform	Trace

the polarized carbonyl group is facilitated. Besides, methylthiol also reacts in an analogous manner with ketones such as acetone, cyclopentanone, and cyclohexanone in the presence of morpholine in dimethylformamide to give dimethylthioketals [13]. However, this hardly explains the varying activities of different bases with the same ketone and the fact that primary amines are, as a rule, better catalysts than secondary amines. It is also not understandable why only cyclohexanone reacts with hydrogen sulfide in the presence of triethylamine. Since the amines act differently, since enamines and ketimines can also be split into dithiols, and since inorganic bases show no catalytic activity, in some cases primary formation of a *gem*-hydroxyamino compound should be considered, this being substituted by SH ion in the following step. We are at present trying to clarify these complicated circumstances.

The formation of thioketones *(2)* observed in some cases is interesting. It is true that some thioketones only arise as secondary products during the distillation by elimination of H_2S from the dithiols *(1)*, but it is not yet known whether this mode of formation is of general validity. Preparatively, the monomeric thioketones are best obtained at present by thermal decomposition of adducts [2, 3].

Base-Catalysed Reaction of Monoketones with H_2S:

A rapid stream of hydrogen sulfide is passed for about 7 h into an ice-cooled solution of 0.5 mole of the ketone in 100 ml of a polar solvent, which has been mixed beforehand with 0.05 mole of the amine catalyst. The mixture is poured onto ice, acidified with dilute hydrochloric acid, and extracted twice with petroleum ether. The extract is washed with water until free from acid, dried with sodium sulfate, and distilled through a 30 cm Vigreux column at a pressure low enough to ensure that the boiling point of the product is below 100 °C. For details, see Table 1. All operations should be carried out under a hood; the outgoing air and waste-water should be purified chemically.

The infrared spectra of the *gem*-dithiols show characteristic SH-absorption at 2555 cm^{-1}.

The Base-Catalysed Action of H_2S on 1,3-Diketones

Whereas monoketones react with hydrogen sulfide in the above manner to give either dithiols or thioketones, 1,3-diketones yield monothiodiketones of type *(3)*. The second carbonyl group is not attacked under the conditions used.

$$R{-}CO{-}CH_2{-}CO{-}R \xrightarrow{H_2S,\ \text{amine}} \underset{(3)\ \ SH}{R{-}CO{-}CH{=}C{-}R}$$

In contrast to the unconjugated, deep red thioketones, these compounds are golden yellow. Their smell is pungent, but less penetrating than that of the simple thioketones. No lead salt is formed with lead acetate, as with other unstable mercapto compounds; instead, lead sulfide separates out. The lack of SH-absorption in the infrared spectrum of *(3)* implies strong chelation. In methanolic sulfuric acid, monothiodiketones *(3)* give dark red mono-2,4-dinitrophenylhydrazones, with retention of the mercapto group.

Base-Catalysed Reaction of Hydrogen Sulfide with 1,3-Diketones:

Here 0.5 mole of the diketone is treated with 0.05 mole of morpholine. Then a rapid stream of hydrogen sulfide is passed into the precipitate, the reaction mixture becoming clear and intense yellow. The reaction is complete after about 7 h. The mixture is diluted with 100 ml of light petroleum, washed with dilute hydrochloric acid, then with water, dried over sodium sulfate, and distilled at a pressure of under 1 mm Hg after removal of the solvent *in vacuo*. For example, 2-mercapto-2-penten-4-one is formed from acetylacetone by this method in 24 % yield; its 2,4-dinitrophenylhydrazone has m.p. 167–168 °C (decomp.).

Base-Catalysed Reduction of 1,2-Diketones with Hydrogen Sulfide

Surprising preparative results, which may also be of great theoretical importance and significance, for example for the Willgerodt reaction, were obtained by the action of hydrogen sulfide, with ice-cooling, on 1,2-diketones in methanol or dimethylformamide in the presence of an amine catalyst. Here *gem*-dithiols or thioketones are not formed; elemental sulfur is eliminated, and depending on the reaction conditions, one of the two carbonyl groups is reduced selectively, to either a methylene group [type *(4)*] or to a secondary alcohol [type *(5)*]. Almost invariably, the reaction proceeds amazingly simply and quantitatively; the second carbonyl group remains unattacked.

$$\underset{(5)}{R{-}CO{-}CH(OH){-}R} \leftarrow R{-}CO{-}CO{-}R \rightarrow \underset{(4)}{R{-}CO{-}CH_2{-}R}$$

Both reduction stages *(4)* and *(5)* are to be regarded as end-products under the given conditions, as *(5)* cannot be converted into *(4)*, and *(4)* cannot be reduced further. Which end-product arises is determined by the amine added and by the solvent. This can be seen for benzil, for example, from Table 4.

Table 4. Dependence of products of reduction with H_2S on solvent and amine.

Amine	Solvent		
	Methanol	Dimethylformamide	None
Pyridine	*(4)*	*(4)*	*(4)*
Morpholine	*(4)*	*(4)* + *(5)*	*(4)* + *(5)*
Piperidine	*(4)* [*]	*(5)* [**]	*(4)* + *(5)*
Aniline	No reaction	*(4)*	No reaction
n-Butylamine	No reaction		
None	No reaction	*(4)*	No reaction

[*] Only 33 % conversion after 7 h.
[**] Quantitative conversion after only 1 h.

In all cases without solvent, addition of pyridine causes a quantitative reduction of the 1,2-diketone to the monoketone *(4)*. The latter is likewise obtained in almost quantitative yield by working with methanol/morpholine or with dimethylformamide/aniline. Methanol/piperidine gives a conversion of only 33 % after 7 h. Without addition of amine, or in the presence of a primary amine, no reaction occurs in methanol.

In a peculiar way, hydrogen sulfide in carefully purified dimethylformamide can reduce the 1,2-diketone quantitatively to the monoketone *(4)* without addition of an amine, whereas in the presence of a secondary amine, only the hydroxyketone *(5)* is formed.

With piperidine, quantitative reduction to *(5)* is complete after only 1 h; in the presence of morpholine a mixture of both reduction products *(4)* and *(5)* is obtained after 4 h. In the absence of solvent, only pyridine, morpholine, and piperidine catalyse the reduction.

Reduction of 1,2-Diketones with Hydrogen Sulfide:

Hydrogen sulfide is passed for up to 4 h into a solution of 0.2 mole of the 1,2-diketone and about 30 ml of amine in methanol or dimethylformamide, the solution being cooled with ice; separation of elemental sulfur occurs during the process. The mixture is acidified with dilute hydrochloric acid, the resulting precipitate filtered off with suction, roughly separated from sulfur by warming gently with methanol, and the reduction product, dissolved by the methanol, purified by recrystallization. Liquid reduction products resulting from acidification are extracted with ether and, after being dried over sodium sulfate, distilled.

Examples:

Benzoin from benzil: Reaction in pyridine/dimethylformamide; H_2S passed in for 1 h; yield quantitative. Identification by analysis, mixed melting-point, 2,4-dinitrophenylhydrazone, and comparison of infrared spectra.

Deoxybenzoin from benzil: Reaction in pyridine/methanol; H_2S passed in for 4 h; yield quantitative. Identification as above.

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Formation and Cleavage of Dihydroxydiarylmethane Derivatives

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Dihydroxydiarylmethane derivatives are formed by condensation of aromatic hydroxy and carbonyl compounds in the presence of acidic condensing agents at low temperatures or in the presence of bases at elevated temperatures. This article deals with formation and cleavage mechanisms in acid and basic media. As a result of the investigations reported, new methods of preparing unsymmetric dihydroxydiarylmethane derivatives and p-alkenylphenols have been developed.

1. Preparation of Dihydroxydiarylmethane Derivatives [*]

The parent compound of the dihydroxydiarylmethane series, 4,4'-dihydroxydiphenylmethane, was first prepared in 1878 by *Beck* [1]. The method used involved alkaline fusion of the corresponding disulfonic acid. *Nölting* and *Herrberg* [2] also prepared it in low yields from phenol and formaldehyde in the presence of dilute mineral acids. In 1891, *Dianin* [3] synthetized 2,2-bis-(*p*-hydroxyphenyl)propane in good yields from phenol and acetone in the presence of strong mineral acids.

For a long time, this readily obtainable substance, also referred to as bisphenol, Bisphenol A or Dian, found no significant industrial application. Large-scale production of Bisphenol A started only after epoxy resins were developed from Bisphenol A and epichlorohydrin in 1938 [4]. This application does not require Bisphenol A of high purity; however, highly purified material is used in the production of aromatic polycarbonates [5].

Besides Bisphenol A, a few 4,4'-dihydroxydiarylmethane derivatives bearing alkyl substituents on the aromatic radicals have also found application; they are used as non-staining antioxidants for natural and synthetic rubber, polyvinyl compounds, and mineral oils [6]. 4,4'-Dihydroxydiphenylmethane derivatives have also been proposed as intermediates for the preparation of phenolic resins and tanning agents.

2,2-Bis-(*p*-hydroxyphenyl)propane possesses estrogenic activity [7]. Other representatives of this class of compounds

[*] Dihydroxydiarylmethane derivatives imply compounds in which two equal or different hydroxyaryl groups are linked to the same carbon atom. This atom can be substituted with hydrogen or an aliphatic or aromatic radical or be a member of a cycloaliphatic ring.

[1] *C. Beck*, Liebigs Ann. Chem. *194*, 318 (1878).

[2] *Nölting* and *Herrberg*, Chemiker-Ztg. *16*, 185 (1892); see also *N. Caro*, Ber. dtsch. chem. Ges. *25*, 947 (1892).

[3] *A. Dianin*, J. russ. physik. Ges. *1891*, 488, 523, 601; Ber. dtsch. chem. Ges. *25*, Ref. 344 (1892).

[4] Swiss Pat. 211116 (1940), Gebr. de Trey A.G., inventor: *P. Castan*; see also *A. M. Paquin:* Epoxydverbindungen und Epoxydharze. Springer, Berlin-Göttingen-Heidelberg, 1958.

[5] *H. Schnell*, Angew. Chem. *68*, 633 (1956); Ind. Engng. Chem. *51*, 157 (1959); Plast. Inst., Trans. and J. *28*, 143 (1960).

[6] US.-Pat. 2515906 (1950), Gulf Res. and Development Co., inventors: *D. R. Stevens* and *A. C. Dubbs*; US.-Pat. 2559932 (1951), I. C. I. Ltd., inventors: *A. S. Briggs* and *J. Haworth*; US.-Pat. 2894004 (1959), Dow Chem. Co., inventor: *A. J. Dietzler*; US.-Pat. 2917550 (1959), Dow Chem. Co., inventor: *A. J. Dietzler*; US.-Pat. 2877210 (1959), Hercules Powder Co., inventor: *R. A. Bankert*.

[7] *G. Bornmann* and *A. Loeser*, Arzneimittel-Forsch. *9*, 9 (1959).

are active against poultry coccidiosis [8]. 4,4'-Dihydroxydiphenylmethane derivatives which are substituted with quinoline or isoquinoline residues on the central carbon atom have a laxative action [9].

a) Synthesis from Aromatic Hydroxy Compounds and Oxo Compounds by Acid-Catalysed Condensation

The condensation of aromatic hydroxy compounds with oxo compounds proceeds with elimination of water. Unless this water is bound or otherwise removed, the condensation stops after low conversions.

The reaction is catalysed by acid condensing agents such as hydrogen chloride, hydrogenbromide, hydrogen fluoride, phosgene, boron trifluoride, aluminum chloride, phosphorus halides, phosphorus pentoxide, phosphoric acid, concd. hydrochloric acid, sulfuric acid, mixtures of glacial acetic acid with acetic anhydride, hydrogen chloride, or sulfuric acid, mixtures of hydrochloric acid with sulfuric acid, and appropriate cation exchangers.

Acid condensation catalysts, such as cation exchangers, that are unable to combine with water give high yields only if the water is removed, for example, by azeotropic distillation, or combined with chemical agents such as $CaCl_2$.

By treating phenol with formaldehyde, paraformaldehyde, trioxane, or methylal in the presence of acid condensing agents such as hydrochloric acid at low temperatures, in addition to 4,4'-dihydroxydiphenylmethane, other isomers, mostly 2,2'- and 2,4'-dihydroxydiphenylmethane, and resinous polycondensation products are obtained. Resin formation is minimized by the use of a large excess of phenol or of dilute mineral acid as solvent. However, the yields of isomeric dihydroxydiphenylmethanes are about 70% at the best, 35% of this being 4,4'-dihydroxydiphenylmethane [10], based on phenol.

Better yields of dihydroxydiphenylmethane derivatives are sometimes obtained when other aliphatic and aromatic aldehydes, *e.g.*, acetaldehyde, n-butyraldehyde, isobutyraldehyde, chloral [11], pyridine-aldehyde [12], or benzaldehyde [13] are condensed with phenol in the presence of acid condensing agents, such as hydrochloric acid or sulfuric acid with a maximum concentration of 70% H_2SO_4. Substantially higher yields of well-defined dihydroxydiphenylmethane derivatives are obtained on acid condensation of 4-, 2,3-, 2,4-, 2,5-, 2,6-, 2,4,5-, or 2,3,4,6-substituted phenols with formaldehyde or other aldehydes [14]. Treatment of unsaturated aldehydes, *e.g.*, acrolein, with phenols in the presence of acid condensing agents at low temperatures yields bis(hydroxyphenyl)alkenes. At temperatures of about 100 °C, these compounds add on more phenol across their double bond so that, depending on molar ratios used, tri- or polyphenols are predominantly formed [15].

Ketones give better yields of well-defined condensation products than aldehydes do. The preferred acid condensing agents are hydrogen chloride, concd. hydrochloric acid, and sulfuric acid having a maximum concentration of 70%. The most efficient would be concentrated sulfuric acid, but its use is precluded by the fact that it causes sulfonation of aromatic hydroxy compounds and dihydroxydiarylmethane derivatives. The 70% sulfuric acid is less efficient than concd. hydrochloric acid, and the latter less than hydrogen chloride. Other acid condensing agents such as BF_3/formic acid used in conjunction with calcium chloride as water acceptor [16], or cation exchangers such as sulfonated, crosslinked polystyrenes [17] have not found any industrial application so far.

The most reactive ketones are acetone [3] and alicyclic compounds such as cyclohexanone [18]. The condensation activity of dialkyl ketones decreases with increasing length of the alkyl radicals [19]. Alkyl aryl ketones and diaryl ketones condense at a slower rate than dialkyl ketones [20].

Ketonic carboxylic acids, *e.g.*, levulinic acid, and aromatic hydroxy compounds can be condensed to give bis-(*p*-hydroxyaryl) compounds in which a carboxyl group is attached to the alkyl radical [21]. Mercaptals undergo condensation much more readily than the corresponding ketones [22].

Surprisingly, acylnitriles such as phenylglyoxylonitrile also undergo condensation with hydroxy compounds in the presence of strongly acid condensing agents, to give

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[8] US.-Pat. 2535015 (1950) and 2538725 (1951), Dow Chem. Co., inventors: *J. E. Johnson* and *D. R. Mussel*.

[9] US.-Pat. 2753351 (1956), Dr. Karl Thomae G.m.b.H., inventors: *A. Kottler* and *E. Seeger*.

[10] US.-Pat. 2812364 (1957), Union Carbide Corp., inventors: *A. G. Farnham* and *F. P. Klosek*; US.-Pat. 2792429 (1957), Union Carbide Corp., inventor: *J. M. Whelan, Jr.*

[11] *H. Pauly* and *H. Schranz*, Ber. dtsch. chem. Ges. *56*, 982 (1923).

[12] Belg. Pat. 518457 (1953), Dr. Karl Thomae G.m.b.H.

[13] *J. Gronowska* and *B. Szpilewski*, Roczniki Chem. *34*, 289 (1960).

[14] *N. J. L. Megson* and *A. A. Dummond*, J. Soc. chem. Ind. *49*, 394 (1930); US.-Pat. 2435593 (1948), Burton T. Bush Inc., inventors: *M. Luthy* and *W. S. Gump*; US.-Pat. 2616932 (1952), Dow Chem. Co., inventors: *C. L. Moyle* and *P. A. Wolf*; US.-Pats. 2796444, 2796445 (1957), American Cyanamid Co., inventor: *F. A. V. Sullivan*; US.-Pat. 2798079 (1957), Universal Oil Products Co., inventor: *C. B. Linn*; US.-Pat. 2932671 (1960), Alco Oil and Chemical Corp., inventors: *O. B. Hager* and *B. Coe*; US.-Pat. 2919294 (1959), Monsanto Chem. Co., inventors: *D. J. Beaver* and *R. O. Zerbe*; US.-Pat. 2912463 (1959), Monsanto Chem. Co., inventors: *D. J. Beaver* and *R. O. Zerbe*; Brit. Pat. 711122 (1952), N.V. de Bataafsche Petroleum Mij., DDR-Pat. 14472 (1958), inventors: *F. Andreas*, *H. Berthold*, and *W. Heidinger*.

[15] German Printed Patent Application 1061791 (1959), Union Carbide Corp., inventor: *A. G. Farnham*.

[16] Belg. Pat. 601797 (1961), Alpine Chemische A.G.

[17] French Pat. 1237656 (1960), Union Carbide Corp., inventors: *F. N. Apel*, *L. B. Conte, Jr.* and *H. L. Bender*; French Pat. 1244533 (1960), Union Carbide Corp., inventors: *F. N. Apel*, *P. Farevaag*, and *H. L. Bender*; Belg. Pat. 589727 (1959), Ciba, S. A.

[18] US.-Pat. 1760758 (1930), General Aniline Works Inc., inventor: *E. Korten*; US.-Pat. 2069560 (1937), E. I. duPont de Nemours Co., inventor: *H. S. Rothrock*; US.-Pat. 2069573 (1937), E. I. duPont de Nemours Co., inventor: *E. K. Bolton*.

[19] *F. V. Morris*, *G. F. Bechtle*, and *T. J. Byerle*, J. Amer. Oil Chemists' Soc. *37*, 646 (1960).

[20] *A. Müller*, Chemiker-Ztg. *45*, 632 (1921).

[21] US.-Pats. 2907736, 2907737 (1959), S. C. Johnson and Son Inc., inventor: *S. O. Greenlee*; US.-Pat. 2933520 (1960), Pittsburgh Plate Glass Co., inventor: *A. R. Bader*.

[22] US.-Pat. 2602821 (1952), Shell Development Co., inventors: *D. B. Luten*, *S. A. Ballard*, and *C. G. Schwarzer*.

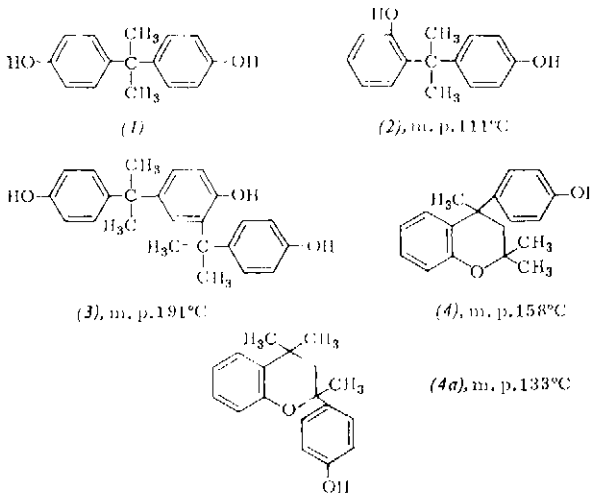
bis-(*p*-hydroxyaryl)arylacetonitriles [23]. The reaction is accelerated by catalytic amounts of ionizable compounds of divalent sulfur such as sulfur dichloride, sodium thiosulfate, hydrogen sulfide, sodium sulfide, thiols, thiophenols, thioacetic acid, thioglycollic acid, mercapto alkyl sulfonic acid or hydroxyalkylthiols [24].

Less pronounced accelerating effects are exhibited by hydrogen selenide and hydrogen telluride [25], ferrous chloride [20], and acid-soluble boron compounds such as boric acid [26,27]. Ultraviolet and γ-radiation are also reported to catalyze the reaction [28]. The reaction is carried out with undiluted reactants [29] or their solutions in inert solvents such as aromatic hydrocarbons [30], chlorinated aliphatic hydrocarbons [31], or glacial acetic acid [3]. High yields result when the molar ratio of aromatic hydroxy compound to ketone is at least 3.7:1 [22]. The condensation should be carried out at the lowest temperature possible, and always below 80 °C, since the formation of by-products increases with increasing temperature [32,33]. The temperature at which the reactants cease to form a homogeneous liquid phase represents a lower limit for condensations carried out in the absence of solvents. Many aromatic hydroxy compounds react with ketones to form crystalline, sharp-melting addition compounds of defined composition [34].

2,2-Bis-(*p*-hydroxyphenyl)propane (Bisphenol A) may be prepared by condensation of phenol and acetone below 70 °C in the presence of sulfuric acid of 70% maximum concentration; thiols or thiocarboxylic acids are added as accelerators. Bisphenol A obtained in this manner must be purified by cumbersome methods which depress the yield considerably.

As a result of increased purity requirements, the use of hydrogen chloride, especially in condensations carried out in indifferent solvents, or of concd. hydrochloric acid is preferred [35]. The acid-catalysed condensation of acetone with phenols yields Bisphenol A *(1)* plus compounds *(2)* to *(4a)* as by-products [36]. Small amounts of *p*-isopropylphenol and resinous products are also obtained.

These by-products, consisting mainly of *(2)*, may amount to 40% or more. Greater amounts are obtained at higher temperatures.



(1)

(2), m. p. 111 °C

(3), m. p. 191 °C

(4), m. p. 158 °C

(4a), m. p. 133 °C

The amount of by-products is substantially lowered if the condensation is carried out so that Bisphenol A or its addition compound with 1 mole of phenol is allowed to crystallize out of the reaction mixture [37]. Condensation of saturated phenol solutions in concd. hydrochloric acid, from which the crystalline addition compound separates out as fast as it is formed, yields Bisphenol A containing less than 2% by-products [38].

Since acid cleavage of cumene hydroperoxide yields phenol and acetone, the use of acids such as hydrogen chloride or hydrochloric acid permits its direct conversion to Bisphenol A. To maintain the proper molar ratio of reactants in the reaction mixture, acetone is removed by distillation or phenol is added [39].

Isolation of pure bis-(*p*-hydroxyaryl)alkanes is achieved by neutralizing the reaction mixture and removing starting materials as well as by-products and solvent. The simplest process involves neutralization of the mineral acids with alkali or preferably with sodium carbonate or bicarbonate solutions, in which phenol and bis-(*p*-hydroxyaryl)-alkanes are insoluble, and then washing of the organic phase until free from electrolytes and fractional distillation *in vacuo* of the products [40]. This procedure is unsatisfactory, however, because decomposition of bis-(*p*-hydroxyaryl)alkanes at high temperatures is accelerated by alkaline impurities and

[23] German Pat. 1075631 (1960), Farbenfabriken Bayer A.G., inventors: *H. Schnell* and *G. Buchwald*.

[24] US.-Pat. 2359242 (1944); Dow Chem. Co., inventors: *R. P. Perkins* and *F. Bryner*; US.-Pat. 2468982 (1949), G. F. Goodrich Co., inventor: *J. E. Jansen*; US.-Pat. 2730552 (1950), 2730553 (1956), 2775620 (1956), N.V. de Bataafsche Petroleum Mij., inventor: *G.T. Williamson*; US.-Pat. 2923744 (1960), Soc. des usines chimiques Rhône-Poulenc, inventors: *I. Scriabine* and *P. M. Bonnart*; French Pat. 1234620 (1960), Feldmühle Papier- und Zellstoffwerke A.G.

[25] US.-Pat. 2762846 (1956), Technical Tape Corp., inventors: *E. J. Reiner, H. S. Schultz, J. G. Schumann*, and *M. Silberberg*.

[26] US.-Pat. 1977627 (1934), I. C. I. Ltd., inventor: *R. Greenhalgh*.

[27] US.-Pat. 1986423 (1935), E. I. duPont de Nemours Co., inventor: *J. A. Arvin*.

[28] US.-Pat. 2936272 (1960), Union Carbide Corp., inventors: *H. L. Bender, N. Apel*, and *L. B. Cante, Jr.*

[29] US.-Pat. 1978949 (1934), Rohm and Haas Co., inventors: *S. Kohn* and *E. Schub*.

[30] Brit. Pat. 428944 (1935), Resinous Products and Chem. Comp.

[31] Brit. Pat. 557976 (1943), Distillers Comp. Ltd., inventors: *H. M. Stanley, J. D. Morgan*, and *W. L. Pritchard*.

[32] US.-Pat. 2191831 (1940), Dow Chem. Co., inventor: *R. P. Perkins*.

[33] US.-Pat. 1977624 (1934), I. C. I. Ltd., inventor: *R. Greenhalgh*.

[34] *J. Schmidlin* and *R. Lang*, Chem. Ber. *43*, 2806 (1910).

[35] Petroleum Refiner, Nov. *1959*, 225.

[36] *W. F. Christopher* and *D. W. Fox:* Polycarbonates. Reinhold Publishing Corp., New York 1962, p. 12.

[37] German Pat. 1027205 (1958), Farbenfabriken Bayer A.G., inventors: *K. H. Meyer* and *H. Schnell*.

[38] Belg. Pat. 480053 (1961), Farbenfabriken Bayer A.G., inventors: *H. Ruppert* and *H. Schnell*.

[39] French Pat. 1060888 (1954), N.V. de Betaafsche Petroleum Mij., inventors: *H. I. Watermann* and *J. P. Fortuin*; US.-Pat. 2669588 (1954), Shell Development Co., inventors: *P. H. Deming* and *H. Dannenberg*; US.-Pat. 2713072 (1955), Shell Development Co., inventor: *H. Dannenberg*; French Pat. 1037198 (1953), Soc. des usines chimiques Rhône-Poulenc.

[40] Brit. Pat. 794476 (1958), Union Carbide Corp., inventors: *R. I. Hoaglin, C. W. Plummer*, and *H. C. Schultze*; US.-Pat. 2182308 (1939), Dow Chemical Co., inventors: *E. C. Britton* and *F. Bryner*.

metal ions. Moreover, isomer separation by distillation is not possible. Thermal decomposition can be markedly reduced by the use of additives such as secondary or tertiary alkaline earth phosphates which inactivate alkaline impurities and bind metal ions [41].

Following removal of unreacted starting materials, *e.g.* by steam distillation, purification can also be accomplished by dissolving the reaction product in alkali and reprecipitating it by acidification. This process is not very effective [42].

More thorough purification is achieved if the condensation product is dissolved in boiling dilute alkali and allowed to crystallize out on cooling. The alkali should neutralize only about $^1/_{20}$ of the aromatic hydroxyl groups [43]. The disadvantage of both methods lies in the sensitivity of alkaline solutions of bis(hydroxyphenyl)alkanes to atmospheric oxygen.

Decomposition is minimized if bis-(*p*-hydroxyaryl)-alkanes or their addition compounds with aromatic hydroxy compounds are purified by crystallization from organic solvents such as benzene, toluene, chlorotoluene, or dichloroethylene. Another suitable solvent is phenol, the crystalline phenol-bis(*p*-hydroxyaryl)alkane addition compound precipitating out from this on cooling [44]. More suitable is a phenol-water mixture which yields addition compounds of high purity [37]. Removal of the phenol by distillation constitutes the best method of cleaving these compounds.

It has also been proposed to extract the condensation product with solvents such as heptane which dissolve only the by-products [45].

b) Synthesis by Alkaline Condensation of Aromatic Hydroxy and Oxo Compounds

The preparation of dihydroxydiarylmethane derivatives by alkaline condensation of aromatic hydroxy compounds with oxo compounds has only slight practical importance. Treatment of unsubstituted aromatic hydroxy compounds with formaldehyde in the presence of alkali gives mixtures of ring substituted mono- and polyhydroxymethyl aromatic hydroxy compounds from which well-defined products either cannot be isolated at all or are obtained only with difficulty. These hydroxymethylphenols react further to give resols [46]. In this reaction, dihydroxydiarylmethane derivatives, among other compounds, are formed as intermediates.

The reaction of solutions of 2,4- or 2,6-dialkylphenols with aliphatic or aromatic aldehydes in the presence of alkali metal hydroxide as condensing agent gives useful yields of dihydroxydiphenylmethane derivatives [47].

Alkaline condensation of hydroxymethyl-substituted phenol derivatives (obtainable from disubstituted phenols such as 2,4-dimethylphenol) with other 2,4- or 2,6-disubstituted phenols leads to unsymmetric dihydroxydiphenylmethane derivatives [48].

Alkaline condensation of aromatic hydroxy compounds with aldehydes is carried out in the absence of water, mostly in aliphatic alcohols, at temperatures up to 130 °C.

Dihydroxydiphenylmethane derivatives are obtained in good yields on treatment of saturated ketones such as acetone and cyclohexanone or acetophenone with phenol or 2- or 2,6-substituted phenols. The reaction is carried out in the presence of an alkali or alkaline earth phenoxide at 100–200 °C. Here, too, the formation of 4,4′-dihydroxydiarylmethane derivatives is favored by an excess of the aromatic hydroxy compound (3–7 moles per mole of ketone); 1.0–2.5 moles of alkali or alkaline earth phenoxide should be used. Larger amounts of phenoxide cause increased formation of resinous by-products [49].

The high reaction temperatures (160–180 °C) and relatively extended reaction times are disadvantageous since, under alkaline conditions, they promote attack by oxygen on the phenols and bisphenols.

2. Other Preparative Methods

a) Reaction of Alkenylphenols with Aromatic Hydroxy Compounds

Compounds with a hydroxyaryl radical attached to a carbon atom which is also linked to another radical by a double bond readily add on aromatic hydroxy compounds to give dihydroxydiarylmethane derivatives. This reaction is exothermic and is catalyzed by acids at low temperatures or by bases at elevated temperatures [50].

Suitable alkenylphenols include 1-(*p*-hydroxyphenyl)-1-propene, 2-(*p*-hydroxyphenyl)-1-propene, 2-(*p*-hydroxyphenyl)-1-butene, 1-(*p*-hydroxyphenyl)-1-phenylethylene, and 1-(*p*-hydroxyphenyl)-1-cyclohexene.

Aromatic hydroxy compounds which undergo the addition are phenol, and alkyl-, aryl-, aralkyl-, cycloalkyl-, halogeno-, alkoxy-, and nitro-substituted phenols and naphthols, provided that they still contain labile hydrogen atoms on the aromatic ring.

In the presence of acid catalysts such as hydrogen chloride, hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid, phosphoric acid, BF_3, $ZnCl_2$, $AlCl_3$, $SnCl_4$, or ion-exchange resins with strongly acidic groups, the reaction

[41] Belg. Pat. 469518 (1960), Farbenfabriken Bayer A.G., inventors: *G. Fritz* and *H. Schnell*.

[42] US.-Pat. 2806068 (1957), Koninklijke Zwavelsuurfabriek N.V., inventor: *J. P. Abrahams*.

[43] Belg. Pat. 611082 (1962), Farbenfabriken Bayer A.G., inventors: *H. Heller, L. Bottenbruch*, and *H. Schnell*.

[44] US.-Pat. 2791616 (1957), Shell Development Co., inventor: *D. B. Luten, Jr.*

[45] US.-Pat. 2845464 (1958), Shell Development Co., inventor: *D. B. Luten, Jr.*

[46] *K. Hultsch:* Chemie der Phenolharze. Springer, Berlin-Göttingen-Heidelberg 1950.

[47] US.-Pat. 2807653 (1957), Ethyl Corp., inventors: *A. H. Filbey* and *T. H. Coffield*; *M. S. Kharasch* and *B. S. Joshi*, J. org. Chemistry *22*, 1435 (1957).

[48] Brit. Pat. 719101 (1954), I. C. I. Ltd.; Belg. Pat. 593606 (1961), Shell Int. Res. Mij., inventors: *R. C. Morris, A. L. Rocklin*, and *R. E. Vincent*.

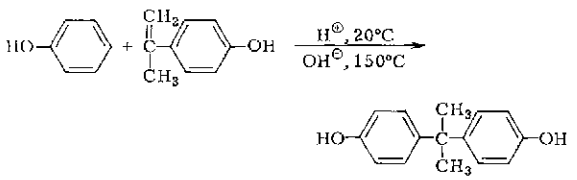
[49] US.-Pat. 2858342 (1958), Union Carbide Corp., inventors: *H. L. Bender, L. B. Conte, Jr.*, and *F. N. Apel*.

[50] Belg. Pat. 487307 (1962), Farbenfabriken Bayer A.G., inventors: *H. Krimm, H. Ruppert*, and *H. Schnell*.

takes place at a satisfactory rate even at or below room temperature. By-product formation increases with rising temperature.

If basic catalysts such as alkali phenoxides, alkoxides, carbonates, or alkali salts of aliphatic or aromatic carboxylic acids are used, the reaction must be carried out at 100–160 °C.

To achieve high yields (≥ 80 %), it is advantageous to use an excess (1–3 moles) of the aromatic hydroxy compound. The same by-products are formed as in the condensation of aromatic hydroxy compounds with oxo compounds. For example, 3 moles of phenol and 1 mole of *p*-isopropenylphenol react together in the presence of 0.006 mole of *p*-toluenesulfonic acid at 20 °C, or of 0.1 mole of sodium phenoxide at 150 °C, to give in a short time 2,2-bis-(*p*-hydroxyphenyl)propane in yields exceeding 80 %.



The reaction mixture is best worked up by neutralizing the catalyst, distilling off the excess of hydroxyaryl compound and purifying the resulting product by crystallization or distillation. Acidic and basic catalysis generally give identical results, but in some cases characteristic differences are noted. Thus the reaction of alkenylphenols with halogenated phenols in the presence of acid catalysts is slow and gives poor yields, whereas a smooth reaction occurs when basic catalysts are used.

Di-, tri-, and polyalkenylphenols also undergo additions with aromatic hydroxy compounds in the presence of acidic or basic catalysts to give dihydroxydiarylmethane derivatives.

The particular advantages of this method lie in the facts that only catalytic amounts of acidic or basic substances are used, that the reaction can be carried out under anhydrous conditions, and that it provides a simple route to well-defined, unsymmetric 4,4′-dihydroxydiarylmethane derivatives.

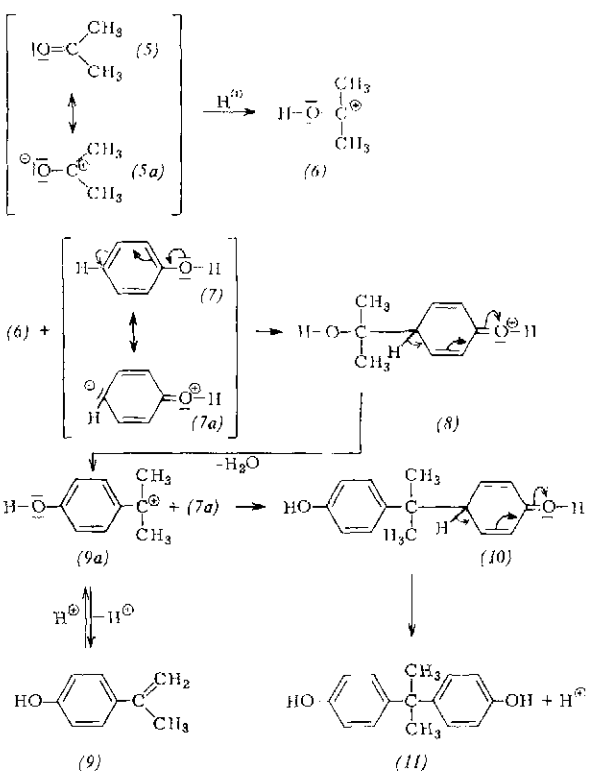
b) Reaction of Olefins with Aromatic Hydroxy Compounds

4,4′-Dihydroxydiarylmethane derivatives are also formed when hydroxyaryl derivatives are allowed to react with compounds which are capable of yielding alkenylphenols under the reaction conditions used. Thus, in the presence of acid catalysts, 1,1-bis-(*p*-hydroxyphenyl)ethane is obtained from acetylene and phenol [51], and 2,2-bis-(*p*-hydroxyphenyl)propane from allene or methylacetylene and phenol [52]. Halogenated alkenes such as 2-chloropropene or 1-chlorocyclohexene [53] and enol esters such as isopropenyl acetate [54] also react with phenol in the presence of strong mineral acids to yield the corresponding 4,4′-dihydroxydiphenylmethane derivatives.

3. Mechanism of Formation of Dihydroxydiarylmethane Derivatives

On the basis of his investigations of the thermal cleavage of 4,4′-dihydroxydiphenylmethane derivatives, *v. Braun* [55] has already postulated that *p*-isopropenylphenol is formed as an intermediate when phenol and acetone react together in the presence of mineral acid to give 2,2-bis-(*p*-hydroxyphenyl)propane.

Since it has been shown in the meantime that alkenylphenols actually do add on aromatic hydroxy compounds in the presence of acid and basic catalysts to yield dihydroxydiarylmethane derivatives, and that the by-products formed in this process are the same as those obtained in the condensation of oxo compounds with aromatic hydroxy compounds, the two-step reaction mechanism postulated by *v. Braun* becomes quite probable. The acid-catalyzed condensation of acetone with phenol to give 2,2-bis-(*p*-hydroxyphenyl)propane is represented in Scheme 1.



Scheme 1. Course of the condensation of acetone with phenol to give 2,2-bis-(*p*-hydroxyphenyl)propane.

A proton adds onto the oxygen of the mesomeric limiting structure *(5a)* of acetone, thereby stabilizing the carbonium structure *(6)*. The quinonoid limiting structure *(7a)* of phenol, with its nucleophilic electron pair in the *para* position, then adds onto the electron-deficient

[51] *J. Furukawa, T. Omae, T. Tsuruta,* and *S. Nakashio,* J. chem. Soc. Japan, ind. Chem. Sect. *60,* 803 (1957); Chem. Abstr. *53,* 10121f (1959); *W. L. Wajsser* and *W. D. Rjabow,* Dokl. Acad. Nauk SSSR *121,* 648 (1958); Erdöl u. Kohle *12,* 657 (1959).

[52] US.-Pat. 2884462 (1959), Union Carbide Corp., inventor: *J. P. Henry.*

[53] US.-Pat. 2602822 (1952), Shell Development Co., inventors: *C. G. Schwarzer* and *D. B. Luten.*

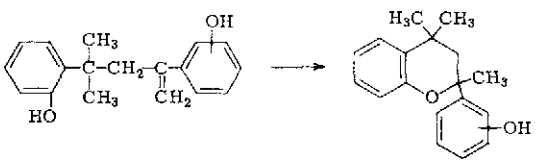
[54] Brit. Pat. 794476 (1958), Union Carbide Corp., inventors: *R. I. Hoaglin, C. W. Plummer,* and *H. C. Schultze.*

[55] *J. v. Braun,* Liebigs Ann. Chem. *472,* 1 (1929); *E. Leibnitz* and *K. Naumann,* Chem. Techn. *3,* 5 (1951).

carbonium ion of the acetone. A protonated carbinol *(8)* is formed which immediately loses water in the acidic medium, yielding a carbonium ion *(9a)*, *i.e.* protonated *p*-isopropenylphenol. This intermediate is a phenylene homologue of protonated acetone. It also appears as an intermediate in the acid-catalysed reaction of isopropenyl phenol *(9)* with phenol. Reaction with another phenol molecule then gives, in analogy with the first reaction step, an addition compound *(10)*, which undergoes aromatization to 2,2-bis-(*p*-hydroxyphenyl)propane *(11)* by elimination of a proton. The deep red-brown transient color of the reaction mixture, observable during acid condensations of phenol with isopropenylphenol or acetone, is most probably caused by the carbonium ion *(9a)*.

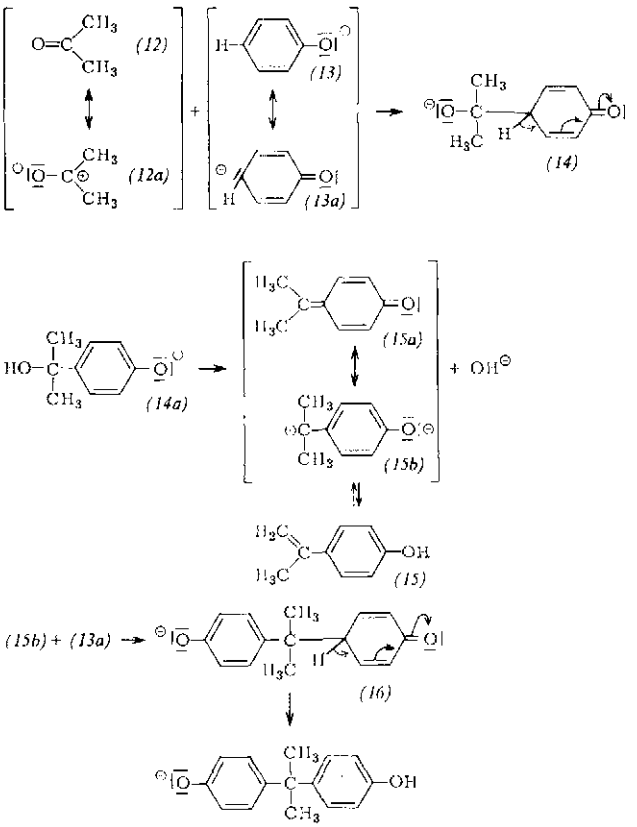
The first of the two reaction steps (condensation of acetone and phenol with elimination of water, and addition of the protonated *p*-isopropenylphenol onto phenol) is rate-determining. The second step is fast and quite exothermic.

Scheme 1 also readily explains the formation of by-products in the condensation of phenol with acetone. Addition of *(9a)* at the *o*-position of phenol leads to 2-(*o*-hydroxyphenyl)-2-(*p*-hydroxyphenyl)propane; addition at the *o*- and *p*-positions gives 2,4-bis-(*p*-hydroxycumyl)phenol *(3)*. Chroman derivatives may arise as a result of ring closure of the dimeric product from two molecules of *o*-isopropenylphenol [56] or from one mole each of *o*- and *p*-isopropenylphenol:



o-Isopropenylphenol does in fact form 2′-hydroxy-2-methyl-4,4-dimethylflavan (m.p. 97 °C) readily in the presence of acid catalysts; an equimolar mixture of *o*- and *p*-isopropenylphenols yields 4′-hydroxy-2-methyl-4,4-dimethylflavan *(4a)*, m.p. 133 °C. 2,2-Dimethyl-4-(*p*-hydroxy)phenyl-4-methylchroman *(4)* is very probably formed by condensation of phenol with mesityl oxide formed in the reaction mixture from acetone. Treatment of mesityl oxide with phenol in the presence of hydrogen chloride readily gives *(4)* in good yields [57]. The base-catalysed condensation mechanism is illustrated in Scheme 2.

The quinonoid limiting structure of the phenoxide ion *(13a)* is stabilized by salt formation and adds onto the electron-deficient position in the resonance hybrid *(12a)* of acetone which has a degenerate double bond yielding the *p*-hydroxyphenylisopropanol anion *(14a)*. This alcohol is also readily obtained from *p*-hydroxyacetophenone and methylmagnesium iodide. It is unstable under the basic condensation conditions and loses the elements of water above 100 °C to yield *p*-isopropenylphenol. In the next step, *p*-isopropenylphenol reacts in the form of a polarized carbonium phenoxide *(15b)* with another phenoxide ion *(13a)* to give *(16)*, which undergoes aromatization via proton and electron shifts



Scheme 2. Base-catalysed condensation of acetone with phenol to give 2,2-bis-(*p*-hydroxyphenyl)propane.

to form the anion of 2,2-bis-(*p*-hydroxyphenyl)propane. Here, too, the same reaction products are obtained as in the base-catalysed condensation of *p*-isopropenylphenol *(15)* with phenol. The fundamental difference between acidic and basic condensation is that the intermediate products with carbonium ion structures such as *(6)* or *(9a)* are more reactive than the quinonoid limiting structures of the phenoxide ion which have a carbanion structure, *e.g. (13a)*.

4. Properties and Analysis of Dihydroxydiarylmethane Derivatives

4,4′-Dihydroxydiarylmethane derivatives are crystalline, high-melting substances; they are insoluble in water but soluble in oxygenated solvents such as alcohols, ethers, and ketones and in hydrocarbons such as cyclohexane, benzene, toluene, and xylene. When undiluted or in acid solution, they are quite stable towards atmospheric oxygen; alkaline solutions discolor in the presence of oxygen. Their water-soluble ammonium salts give off ammonia slowly at room temperatures and rapidly at elevated temperatures.

Quantitative analysis of dihydroxydiarylmethane derivatives can be accomplished by bromometric and potentiometric titration. Their purity can be tested by melting and solidification point determinations. Paper and thin-layer chromatography can be used to separate bis-(*p*-hydroxyphenyl)alkanes from their by-products. Many of them can be characterized by their colors on coupling with diazonium salts and identified by their infrared spectra.

5. Cleavage of Dihydroxydiarylmethane Derivatives

4,4′-Dihydroxydiarylmethane derivatives undergo thermal and hydrolytic cleavage [55]. On heating above

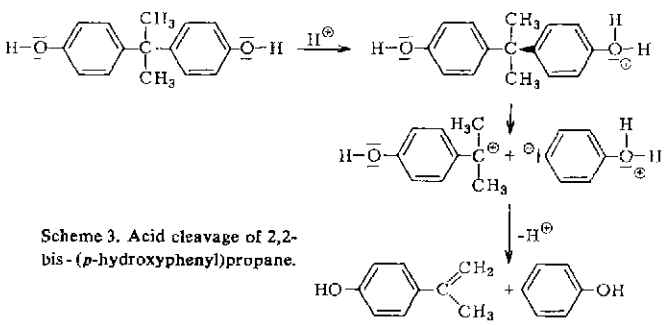
[56] *W. Baker, R. F. Curtis,* and *J. F. W. McOmie,* J. chem. Soc. (London) *1952*, 1774.

[57] *A. Dianin,* Zhurn. russ. fiz.-khim. Obshch. *46*, 1310 (1914).

250 °C at normal pressure or under reduced pressure, they give rise to aromatic hydroxy compounds, alkenyl- and alkyl-substituted aromatic hydroxy compounds, and non-distillable resinous products. Thermal cleavage of Bisphenol A gives phenol, *p*-isopropylphenol, and resinous substances. The isopropylphenol is produced by disproportionation of the isopropenylphenol initially formed. On the other hand, thermal cleavage of 1,1-bis-(*p*-hydroxyphenyl)cyclohexane also yields the substantially more stable olefin 1-(*p*-hydroxyphenyl)-1-cyclohexene in addition to phenol [55].

Acidic and basic compounds markedly reduce the temperature of decomposition. In the presence of acid compounds such as sulfuric acid, *p*-toluenesulfonic acid, zinc chloride, potassium bisulfate, or acidic Fuller's earth, bis-(*p*-hydroxyaryl)alkanes undergo cleavage at temperatures just above 150 °C, even under completely anhydrous conditions. Approximately 1 mole of the corresponding aromatic hydroxy compound is formed per mole of Bisphenol A together with alkenylphenols [58], their polymerization products, alkylphenols, and indeterminate resinous products. Particularly stable alkenylphenols such as 1-(*p*-hydroxyphenyl)-1-cyclohexene can be obtained in useful yields.

The mechanism of acid cleavage is best illustrated by Scheme 3.



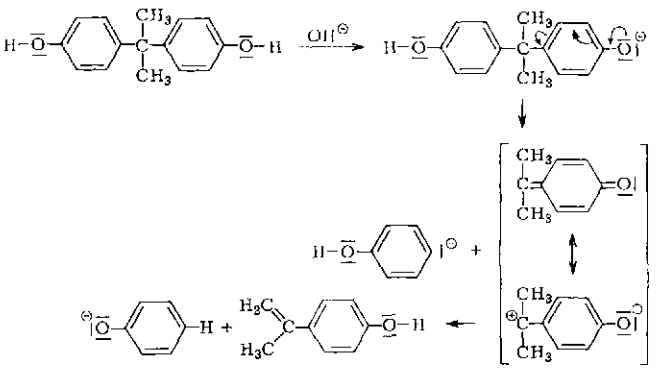
Scheme 3. Acid cleavage of 2,2-bis-(*p*-hydroxyphenyl)propane.

Addition of a proton or a Lewis acid to the phenolic hydroxyl group weakens the bond with the central carbon atom. Ion stabilization after cleavage gives *p*-isopropenylphenol and phenol. At the same temperature, *p*-cumylphenol is correspondingly cleaved into α-methylstyrene and phenol. In the cleavage with acid the protons attack not only the free hydroxyl groups but also the ester and ether groups. Thus the monoacetate of Bisphenol A is cleaved into phenyl acetate and *p*-isopropenylphenol, the diacetate into phenyl acetate and (*p*-isopropenyl)phenyl acetate, and (*p*-cumyl)phenyl acetate into phenyl acetate and α-methylstyrene. In all these cases, the cleavage temperature is below 200 °C.

Cleavage with base of 4,4'-dihydroxydiphenylmethane derivatives above 170 °C takes place much more readily, giving well-defined products in high yields [59]. In this reaction, only equimolar amounts of alkenylphenols and phenols are generally obtained. Since basic catalysis promotes side reactions such as alkenylphenol disproportionation and polymerization to only a minor degree, alkenylphenols can be isolated in yields of over 90%.

This represents a simple route to a large number of *p*-alkenylphenols. A typical example is the alkaline cleavage of Bisphenol A, described below.

Bisphenol A is heated to 170–230 °C at 15 mm Hg in the presence of a basic catalyst (0.01–1.0% sodium hydroxide, carbonate, phenoxide, or acetate). A mixture of *p*-isopropenylphenol (b.p. 120 °C/10 mm Hg) and phenol distils over, and is then separated by fractional distillation. The yield of *p*-isopropenylphenol (m.p. 84 °C) exceeds 90%.



Scheme 4. Alkaline cleavage of 2,2-bis-(*p*-hydroxyphenyl)propane.

The mechanism of the cleavage with base is illustrated in Scheme 4. Abstraction of a proton from one hydroxyl group of Bisphenol A facilitates the formation of a quinonoid limiting structure by electron displacement. As a result, the bond between the central carbon atom and the other aromatic residue is weakened. Finally, phenol is split off in the form of an isomeric phenoxide. The quinone methide, which is also formed, and the carbonium phenoxide represent resonance hybrids of *p*-isopropenylphenol, which arise from the latter by proton displacement.

In agreement with this mechanism, the monoacetate of 2,2-bis(-*p*-hydroxyphenyl)propane undergoes cleavage in the presence of base to give phenyl acetate and *p*-isopropenylphenol, whereas the diacetate is stable under these conditions. *p*-Cumylphenol and (*p*-cumyl)phenyl acetate are stable in the presence of basic catalysts upto 300 °C.

In the presence of aqueous alkali hydroxide at high temperatures, 4,4'-dihydroxydiphenylmethane derivatives are not hydrolysed to the alcohols but, instead, to ketonic compounds and phenols [60]. Heating 2,2-bis-(*p*-hydroxy-phenyl)propane with aqueous sodium hydroxide at 240°C under pressure gives acetone and phenol in good yield.

The reductive cleavage of 4,4'-dihydroxydiphenylmethane derivatives with heavy metal catalysts leads to *p*-alkylphenols and phenols. Thus, on hydrogenation in the liquid phase [61] at 160 °C with a nickel-containing bismuth catalyst, or in the vapor phase [62] at 330 °C with nickel-copper sulfide catalysts on chromic oxide-alumina carriers, 2,2-bis-(*p*-hydroxyphenyl)propane gives *p*-isopropylphenol and phenol in high yields.

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German version: Angew. Chem. 75, 662 (1963).

[58] *B. B. Corson* et al., J. org. Chemistry *23*, 544 (1958).

[59] Belg. Pat. 503367 (1960), Farbenfabriken Bayer A.G., inventors: *H. Krimm* and *H. Schnell*.

[60] German Patent 1094759 (1960), Farbenfabriken Bayer A.G., inventors: *K. H. Meyer* and *H. Schnell*.

[61] German Patent 467640 (1928), Schering-Kahlbaum A.G., inventor: *H. Jordan*; German Patent 479352 (1929), Schering-Kahlbaum A.G., inventor: *H. Jordan*.

[62] German Patent 1105428 (1961), Farbenfabriken Bayer A.G., inventors: *G. v. Schuckmann* and *H. Schnell*.

Syntheses Using Pyridinium Salts (IV) [*]

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Cleavage of N-phenylpyridinium or N-vinylpyridinium salts with secondary aliphatic amines leads to aromatic amino compounds or enamines which are often unobtainable by other routes. The other fragment, glutacondialdehyde or its monoanil, gives azulenes, as shown by Ziegler and Hafner, as well as König; these compounds can also be prepared from alkylpyridinium salts with cyclopentadienylsodium (Hafner). Syntheses of labile aldehydes which are otherwise difficult to obtain and of α-ketocarboxylic acids, starting from pyridinium salts and proceeding via nitrones or α-cyanoanils, are illustrated by many new examples. Benzimidazoles, benzothiazoles, and amidines are accessible from pyridinium salts via nitrones or α-cyanoanils; cyanoanils can be transformed into quinoxalines (including xanthopterine), perimidines, etc. Furthermore, nitrosonaphthols and nitrosonaphthylamines react with pyridinium salts containing an active methylene group on the nitrogen, leading to new ring systems. Further synthetic possibilities arise from nucleophilic displacements of the pyridine in pyridinium salts by S_N2 reactions. Combination of the route via nitrones with the methods of Arndt-Eistert, Ortoleva-King, or with chloromethylation constitutes a significant enlargement of its range of application. The formation of α-cyanoanils from diazoketones permits synthesis of α-keto-β-amino acids from α-amino acids, or of phenylglyoxylic acids from benzoic acids by chain extension.

I. Syntheses involving cleavage of the pyridinium ring
  1. Cleavage to give amino compounds
  2. Azulene syntheses

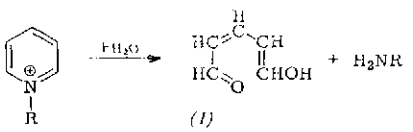
II. Syntheses *via* nitrones
  1. General discussion of the method
  2. Examples from the literature since 1953
  3. Combinations with other methods
    a) Combination with the Arndt-Eistert method
    b) Combination with chloromethylation
    c) Combination with the Ortoleva-King method
    d) *P. Karrer*'s variant
  4. Spontaneous decomposition of nitrones
  5. Syntheses with nitrones
    a) Benzimidazoles
    b) Benzothiazoles
  6. New ring systems from amino- and hydroxy-nitroso-aromatics

III. Syntheses *via* α-cyanoanils (including nucleophilic exchange reactions on pyridinium salts)
  1. *p*-Dimethylaminoanils of benzoyl cyanides
  2. Benzoylglyoxylonitrile *p*-dimethylaminoanils
  3. Other α-keto-α-cyanoanils

I. Syntheses Involving Cleavage of the Pyridinium Ring [**]

1. Cleavage to Give Amino Compounds

It is well known that *Zincke* [1] succeeded in cleaving the pyridine ring in a pyridinium salt, specifically *N*-2,4-dinitrophenylpyridinium chloride; *König* [2] accomplished this independently with *N*-cyanopyridinium bromide. The products were glutacondialdehyde *(1)* or its derivatives, the nitrogen remaining as an amino group in the quaternizing residue [3].



(1)

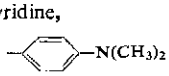
(R = 2,4-dinitrophenyl, CN, or another strongly electron-attracting group)

This cleavage has synthetic applicability in two main directions:

1. The introduction of an amino group by this method can be utilized for preparative purposes.

[*] Communication No. III: *F. Kröhnke*, Angew. Chem. internat. Edit. *2*, 225 (1963).

[**] In this paper, the following abbreviations are used:
Py is frequently used for pyridine,

$Py^{\oplus}$ for , Ar′ for  ,

ON–Ar′ for *p*-nitrosodimethylaniline.
Ph is frequently used for C_6H_5.
Anions such as $Br^{\ominus}$, $ClO_4^{\ominus}$ are frequently omitted where they take no part in the course of reaction.

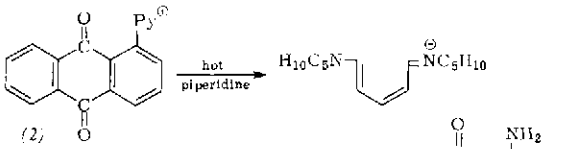
[1] *Th. Zincke*, Liebigs Ann. Chem. *330*, 311, 361 (1904); *338*, 121 (1905); *339*, 193 (1905); *Th. Zincke*, *G. Heuser*, and *W. Möller*, ibid. *333*, 296 (1904); *Th. Zincke* and *W. Würker*, ibid. *338*, 107 (1905); *341*, 371 (1905) and later publications.

[2] *W. König*, J. prakt. Chem. (2) *69*, 105, 134 (1904); *70*, 19 (1904).

[3] *W. König* and *G. A. Becker*, J. prakt. Chem. (2) *85*, 353 (1912); *W. König G. Ebert* and *K. Centner*, Ber. dtsch. chem. Ges. *56*, 751 (1923). For examples of cleavage of the pyridinium ring without elimination of the nitrogen see *Th. Zincke*, Liebigs Ann. Chem. *338*, 311 (1904); *G. Schwarzenbach* and *R. Weber*, Helv. chim. Acta *25*, 1628 (1942); *W. König*, Angew. Chem. *66*, 149 (1954); *N. E. Grigor'eva* and *J. K. Gintse*, Zh. obshch. Khim. *28*, 1682 (1958).

2. The glutacondialdehyde can be incorporated (generally in the nascent state) as a pentamethine chain into other compounds.

With regard to the first application, as briefly mentioned in the first paper of this series [4], *N*-vinylpyridinium salts are cleaved on treatment with hot aqueous piperidine to give enamines, the pentamethine chain of the pyridine being ejected as glutacondialdehyde, which is obtained in the form of its dipiperidide. The enamines



(2)
Anthraquinone-1-pyridinium chloride

1-Aminoanthraquinone

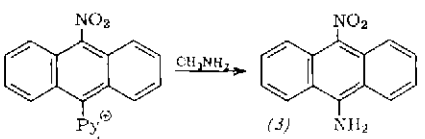
react with acids to give deoxybenzoins in quantitative yields [5]. It appears, in the meantime, that this cleavage reaction has been known in principle for a much longer time – albeit only with pyridinium salts containing a condensed aromatic residue attached to the pyridinium nitrogen. – In an I.G.-Farbenindustrie patent of 1932 [6], the preparation of amino derivatives of anthracene, anthraquinone, and other condensed cyclic compounds is disclosed; they are formed from the corresponding pyridinium salts, *e.g. (2)*, by treatment with basic reagents.

Under certain conditions, this cleavage of pyridine occurs even at 0 °C [6a]; often the C_5 chain of the pyridine nucleus is detached from the pyridinium nitrogen at only one of its two points of attachment.

Preparation of 1,5-Diaminoanthraquinone [6]

About 50 g of piperidine are added to a solution of 10 g of 1,5-bispyridinioanthraquinone chloride in 200 ml of water; the solution is boiled for a short time until the cleavage to 1,5-diaminoanthraquinone is complete. Precipitation of the product in pure crystalline form is completed by cooling the solution.

Hünig and *Requardt* [7] prepared the otherwise inaccessible compound 9-nitro-10-aminoanthracene *(3)* for the first time from 9-nitro-10-pyridinioanthracene chloride and methylamine:

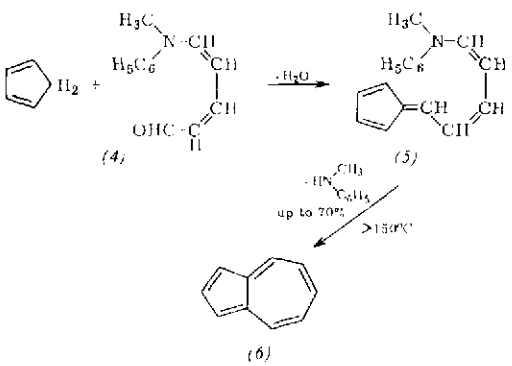


(3)

Concerning the second of the above applications, the possibility of utilizing the pentamethine chain of glutacondialdehyde for the synthesis of cyanines has already been referred to [8]. The third communication reported the introduction of this chain into phenacylpyridinium salts to form new types of anionic cyanines [8a].

2. Azulene Syntheses

Azulene syntheses, based on an idea of *Ziegler* [9] and accomplished by him, and particularly by *Hafner* [10], have aroused considerable interest. The same basic concept is also contained in independent work by *König* and *Rösler* [11]. Thus, *N*-methylanilino-1,3-pentadien-5-al (Zincke's aldehyde), which is formed by cleavage of *N*-cyanopyridinium or *N*-(2,4-dinitrophenyl)pyridinium halide with methylaniline, condenses with cyclopentadiene in the presence of alkali to yield the fulvene derivative *(5)*, which is transformed above 150 °C to azulene *(6)* in yields of up to 70 %, with simultaneous elimination of methylaniline:



(4) *(5)* *(6)*

Substituted cyclopentadienes can also be used. In place of Zincke's aldehyde, 1-diethylamino-1,3-pentadien-5-al can be readily synthetized and used [12]; this compound is obtained from *N*-(2,4-dinitrophenyl)pyridinium chloride with two moles of diethylamine.

Preparation of 1-Diethylamino-1,3-pentadien-5-al [12, 13]

A mixture of 140.8 g (0.5 mole) of *N*-(2,4-dinitrophenyl)-pyridinium chloride and 73.1 g (1 mole) of diethylamine in 300 ml of ethanol is heated for one hour under reflux, and the cooled red solution is poured into 600 ml of water. A precipitate of 2,4-dinitroaniline is obtained. The filtrate is freed from most of the alcohol *in vacuo*, and after one further filtration is allowed to stand for one hour with 120 ml of 20 % sodium hydroxide. The free diethylamine is removed by vacuum distillation, and the residue is extracted several times with small portions of chloroform; the combined chloroform extracts are washed with water and dried with sodium sulfate.

[4] *F. Kröhnke*, Angew. Chem. *65*, 620 (1953), top of left-hand column.

[5] *F. Kröhnke* and *I. Vogt*, Liebigs Ann. Chem. *589*, 26, 45 (1954).

[6] German Pat. 592202 (Jan. 18th, 1934), inventors *W. Mieg*, *R. M. Heidenreich*, and *H. Neresheimer*; Frdl. Fortschr. Teerfarb. Fabrikat. *1933*, II, 1315.

[6a] See *F. Kröhnke*, Angew. Chem. internat. Edit. 2, 229 (1963), Section I, 3, formulae *(24)* → *(25)*.

[7] *S. Hünig* and *K. Requardt*, Angew. Chem. *68*, 152 (1956).

[8] *F. Kröhnke*, Angew. Chem. *65*, 626 (1953), top of left-hand column.

[8a] *F. Kröhnke*, Angew. Chem. internat. Edit. 2, 227 (1963), Section I, 2.

[9] *K. Ziegler*, Angew. Chem. *67*, 301 (1955); Review: *K. Hafner*, Angew. Chem. *70*, 419 (1958).

[10] *K. Hafner*, Liebigs Ann. Chem. *606*, 79 (1957).

[11] *W. König* and *H. Rösler*, Naturwissenschaften *42*, 211 (1955).

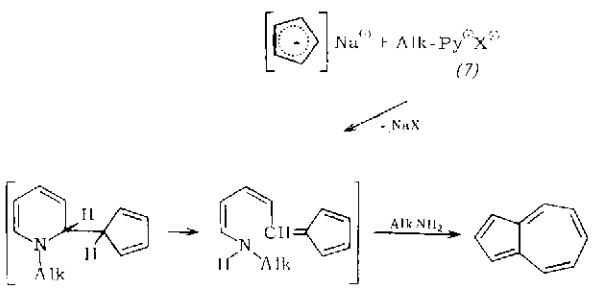
[12] *K. Hafner* and *Kl.-D. Asmus*, unpublished results; *Kl.-D. Asmus*, Ph. D. thesis, Universität Marburg, 1960. I wish to thank Prof. *Hafner*, Munich, for kindly placing this thesis at my disposal.

[13] See also *J. L. Knunjantz* and *T. Ya. Kefeli* Zh. obshch. Khim. *15*, 628 (1945); Chem. Abstr. *40*, 6079 (1946).

A red oil remains after removal of the chloroform and distills at 90–100 °C and 0.001 mm Hg, giving a yellow-orange viscous oil; the yield is 39 g (50.8 %).

The possibilities of applying this reaction to substituted pyridines and thus obtaining azulenes which are substituted in the seven-membered ring are apparently strictly limited. Nevertheless, 6-methylazulene can be prepared from γ-picoline; the synthesis of 5-methylazulene from β-picoline is somewhat easier; both compounds are obtained in a modest overall yield [12]; neither compound is readily available by other means.

Thus, *Hafner* [14] managed to obtain azulene directly from *N*-alkylpyridinium salts *(7)* and cyclopentadienylsodium at 200 °C, using benzidine as a high-boiling



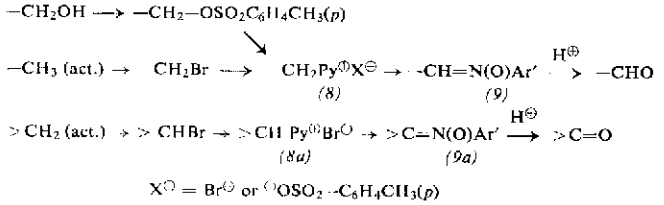
basic solvent; for example, *N*-methyl-2-methyl-5-ethylpyridinium bromide and methylcyclopentadienylsodium afforded 1,4-dimethyl-7-ethylazulene (chamazulene) [15].

Substituted azulenes are formed from pyrylium salts and cyclopentadienylsodium even at 20 °C and in yields as high as 95 % [16]. This even simpler and smoother azulene synthesis requires pyrylium salts which are substituted at positions 2, (4), and 6. Thus, it by no means renders the synthesis from pyridinium salts superfluous; the latter remains important for the preparation, for example, of chamazulene, lactaroviolin, and guaiazulene.

II. Syntheses via Nitrones

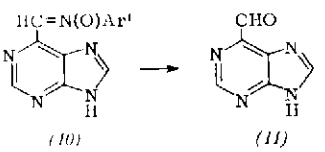
1. General Discussion of the Method

The four-step synthesis [17] of carbonyl compounds from methyl or methylene compounds or from primary alcohols by way of pyridinium salts *(8)* and *(8a)* and nitrones *(9)* and *(9a)* has found wide application in recent years. All four steps proceed even at low temperature (0–20 °C), and the method is therefore especially suitable for the preparation of sensitive aldehydes which are otherwise difficult to obtain; it may



also be used for the synthesis of unsaturated aldehydes, dialdehydes, α-keto-aldehydes, and aromatic ketones. The yields are generally good. The nitrones usually need not be isolated. For the preparation of aromatic aldehydes, particularly those with (+I)-substituents, the Sommelet reaction [18] is generally preferred. Alternatively, the method of *Hass* and *Bender* [19], in which benzyl halides are treated with the sodium salt of 2-nitropropane, may be used. Saturated aliphatic aldehydes are not accessible *via* nitrones up to the present, but there are sufficient other satisfactory methods available for their synthesis.

The presence of pyridine is often advantageous for effective preparation of nitrones [20]. Acidic cleavage of the nitrone has occasionally caused difficulties; hence, a method introduced by *Giner-Sorolla, Zimmermann,* and *Bendich* [21] may be of value. The nitrone *(10)*, which gave only a 4 % yield of aldehyde *(11)* when cleaved with 1 N hydrochloric acid, was converted to the hydrazone in 87 % yield by means of 20 % aqueous hydrazine hydrate, after removal of the *p*-dimethylaminophenylhydroxylamine hydrochloride by filtration. The hydrazone was then converted with ethyl nitrite/hydrochloric acid at 0 °C to very pure aldehyde in 67 % yield (based on the hydrazone). This procedure is adapted from a method of *von Auwers* [22].



Preparation of Purine-6-carboxaldehyde Hydrazone; the Hydrazone of (11) [21]

A suspension of 0.4 g (1.4 mmole) of purine-6-carboxaldehyde *p*-dimethylaminophenylnitrone *(10)* in 5 ml of water is acidified with 5 ml of 2 N hydrochloric acid. *p*-Dimethylaminophenylhydroxylamine hydrochloride precipitates out and is filtered off. The filtrate is heated for 5 min at 80 °C, and sufficient 20 % aqueous hydrazine solution is then added to bring the pH up to 7; an additional 0.75 ml is then added. After cooling, the yellow precipitate, which is formed at once, is removed by filtration, and is washed with some cold water. The yield of hydrazone is 0.2 g (87 %); m.p. of the bright, cream-colored needles after several recrystallizations from alcohol: 255 °C (decomp.).

[14] *K. Hafner*, Angew. Chem. *67*, 302 (1955); *K. H. Heinlein*, Ph.D. thesis, Universität Marburg, 1958.

[15] *K. Hafner*, Angew. Chem. *70*, 421 (1958).

[16] *K. Hafner* and *H. Kaiser*, Liebigs Ann. Chem. *618*, 140 (1958).

[17] *F. Kröhnke* and *E. Börner*, Ber. dtsch. chem. Ges. *69*, 2006 (1936); *F. Kröhnke*, ibid. *71*, 2583 (1938); German Pat. 755943 (June 22nd, 1953); Chem. Zbl. *1955*, 3251; *F. Kröhnke*, Angew. Chem. *65*, 612 (1953); *Houben-Weyl:* Methoden der organischen Chemie. 4th Ed., Thieme, Stuttgart 1954, Vol. VII/1, pp. 200 et seq. *H. Krauch* and *W. Kunz:* Namenreaktionen der Organischen Chemie. Hüthig, Heidelberg 1960, p. 282; *A. R. Surrey:* Name Reactions in Organic Chemistry. 2nd Ed., Academic Press, New York, London 1961, p. 222; Org. Reactions *8*, 203 (1954).

[18] See Org. Reactions *8*, 203 (1954).

[19] *H. B. Hass* and *M. L. Bender*, J. Amer. chem. Soc. *71*, 1767 (1949); Org. Syntheses *30*, 99 (1950).

[20] *F. Kröhnke* and *G. Kröhnke*, Chem. Ber. *91*, 1475 (1958).

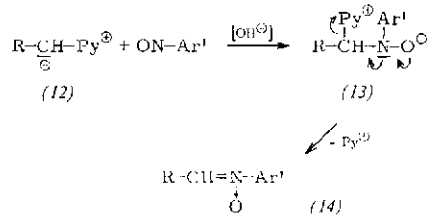
[21] *A. Giner-Sorolla, J. Zimmermann,* and *A. Bendich*, J. Amer. chem. Soc. *81*, 2515, 2518, 2519 (1959).

[22] *K. v. Auwers* and *B. Ottens*, Ber. dtsch. chem. Ges. *58*, 2067 (1925), used semicarbazones. – *E. Kober* and *Chr. Grundmann*, J. Amer. chem. Soc. *80*, 5547 (1958), liberated an aldehyde of the triazine series from its hydrazone with 2,4-dinitrobenzaldehyde ("transcarbimation").

Preparation of Purine-6-carboxaldehyde Hydrochloride; the Hydrochloride of (11) [21]

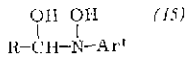
Two ml of ethyl nitrite are added at 0 °C, with stirring, to a cold (0 °C) solution of 0.6 g (3.6 mmoles) of the above hydrazone in 3 ml of 1 N hydrochloric acid and 4 ml of aqueous ethanol. This reaction mixture is stirred for 5 minutes at 0 °C, filtered, and the solvent removed by vacuum distillation; the residue obtained is treated with 10 ml of 50 % ethanol, evaporated to dryness *in vacuo*, and washed with cold alcohol. The yield of hydrochloride is 0.5 g (67 %) of thin, colorless platelets, which sinter at 235–240 °C and melt with decomposition above 350 °C.

The pyridinium salt *(8)* or its betaine *(12)* probably reacts first with the electrophilic *p*-nitrosodimethylaniline to give the "aldol" *(13)*, in which the lone pair of electrons on the hydroxylamine nitrogen exerts an electron pressure on the methine group. In this way, the pyridinium nucleus can capture the bonding electron pair in the manner typical of syntheses involving pyridinium salts. The remainder of the



(12) *(13)* *(14)*

molecule becomes stabilized as the nitrone *(14)*. However, it is also possible that the pyridinium cation is displaced in an S_N2 reaction by hydroxyl ion; a nitrone hydrate *(15)* would then be formed first. Its appearance in this reaction has in

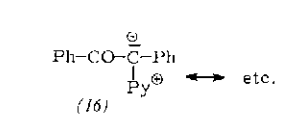


(15)

fact been occasionally observed [23]. Analogously, other nucleophilic anions, *e.g.* $CN^{\ominus}$ or $NC_5H_{10}^{\ominus}$, are able to displace the pyridinium cation, as is shown below.

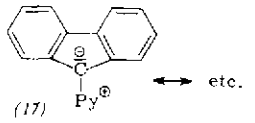
It is especially noteworthy that the preparation of nitrones starting from benzylpyridinium salts is more favorable than that starting from benzyl halides, even though the former route requires an additional step. Some very reactive methyl groups (*e.g.* those in 9-methylacridine or 2,4-dinitrotoluene) or methylene groups (in benzyl cyanide, *etc.*) react directly with nitrosodimethylaniline to yield anils or nitrones. Only in these relatively rare cases is the detour *via* the pyridinium salts unnecessary.

N-Methylenepyridinium salts which give a positive picryl chloride or chloranil reaction [24] react more or less rapidly with nitrosodimethylaniline/NaOH solution as well. In contrast, *N*-methinepyridinium betaines, such as *(16)*, *(17)*, or *(18)*, never undergo these color reactions; however, if the carbon atom of the betaine grouping is sufficiently negative, they will nevertheless react very readily with nitrosoaromatics / NaOH [25].



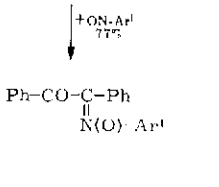
(16)

Desylpyridinium betaine [25]

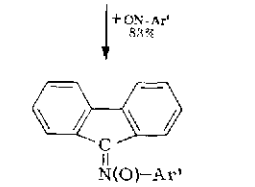


(17)

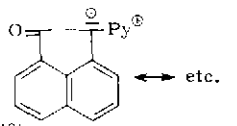
Fluorenylpyridinium betaine [25]



Benzil monoarylnitrone

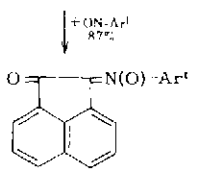


Fluorenone arylnitrone



(18)

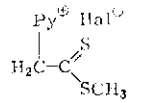
Acenaphthenonylpyridinium betaine [26]



Acenaphthenequinone monoarylnitrone

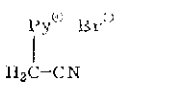
If a compound $RCH_2Py^{\oplus}Hal^{\ominus}$ contains strongly electron-attracting substituents in R, or as R itself or in the pyridinium nucleus – that is, substituents exerting a strong (–I)-effect – nitrones are formed on addition of nitrosodimethylaniline even in neutral alcoholic solution. The nitrone is produced with especial ease if it is stabilized by resonance (hence *not* with nitrosobenzene). This is the case, for example, with the salts *(19)* to *(22)*.

In addition to the nitrone, pyridine hydrobromide is also formed, and the solution becomes acidic.



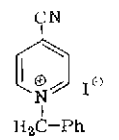
(19)

Methyl pyridiniodithioacetate halide [27]



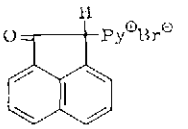
(20)

N-(Cyanomethyl)-pyridinium bromide [28]



(21)

N-Benzyl-4-cyanopyridinium iodide [29]



(22)

Acenaphthenonylpyridinium bromide [26]

[23] *F. Kröhnke* and *E. Börner*, Ber. dtsch. chem. Ges. *69*, 2007, 2010 (1936); *L. Havenith*, Diploma thesis, Universität Gießen, 1954, pp. 13, 14.

[24] *F. Kröhnke*, Angew. Chem. *65*, 606 (1953), right-hand column.

[25] *F. Kröhnke*, Ber. dtsch. chem. Ges. *71*, 2587 (1938): Diphenylmethylpyridinium bromide; ibid. *72*, 534 (1939): Desylpyridinium bromide; Chem. Ber. *83*, 256 (1950): Fluorenylpyridiniumbromide.

[26] *F. Krollpfeiffer* and *L. Havenith*, unpublished results; *L. Havenith*, Ph. D. thesis, Universität Gießen, 1956, pp. 12, 13, 45. The nitrone is formed here even without addition of alkali.

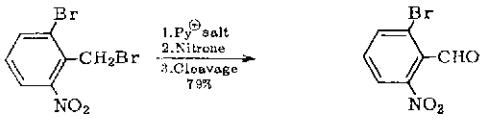
[27] *F. Kröhnke* and *Kl. Gerlach*, Chem. Ber. *95*, 1107 (1962); *Kl. Gerlach*, Ph. D. thesis, Universität Gießen, 1960.

[28] *F. Kröhnke* and *A. Peuser*, unpublished results; see *A. Peuser*, Ph. D. thesis, Universität Gießen, 1962.

[29] *F. Kröhnke* and *B. Sander*, unpublished results; see *B. Sander*, Ph. D. thesis, Universität Gießen, 1961, pp. 29, 77.

2. Some Examples from the Literature since 1953

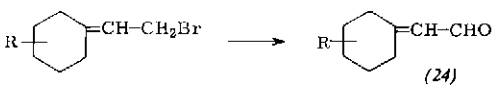
a) *o,o'*-Disubstituted aromatic aldehydes, which were unobtainable by other methods have become accessible from the corresponding benzyl halides, *e.g. (23)* [30]. In this manner,



(23) 2-Bromo-6-nitrobenzaldehyde

2,6-dinitro- (58 %), 2,6-dichloro- (50 %), 2-nitro-4-chloro- (57 %), and 2-nitro-6-chlorobenzaldehyde (75 %) have also been synthetized. The yields (15–20 %) of monofluorobenzaldehydes were no better than those obtained by other methods. *o,o'*-Disubstituted aldehydes appear to be unobtainable *via* bis-nitrones [31].

b) Cyclohexylideneacetaldehyde *(24)* was obtained in about 40 % yield from β-cyclohexylideneethyl bromide [32], which in turn was synthetized from cyclohexanone. Methylated derivatives were also prepared.

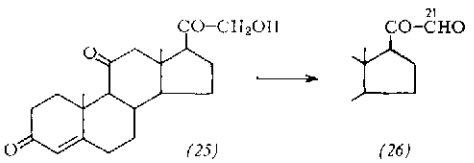


(24)

R = H or 2-, 3- or 4-methyl

c) The preparation of cortisone-21-aldehyde and the 21-aldehydes of cortisone derivatives and hydrocortisone derivatives [33], as well as the transformation of 11-dehydrocorticosterone *(25)* to Δ4-pregnen-21-al-3,11,20-trione hydrate *(26)* has also been accomplished [33].

Beyler and *Hoffmann* [34] succeeded in preparing the α-ketoaldehyde *(26)*, not via the pyridinium salt, nitrone, *etc.*, but much more effectively from the alcohol by oxidation in methanol at 60 °C with copper(II) acetate and a trace of glacial acetic acid.



(25) *(26)*

d) *Ried* and *Königstein* [35] obtained 1,3,5-triformylbenzene (benzene-1,3,5-tricarboxaldehyde) from 1,3,5-trimethylbenzene via the tripyridinium salt (formed in 85 % yield) and the trinitrone (88 %). The aldehyde was formed from the nitrone in a yield of 75 %.

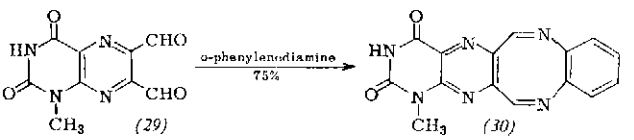
e) Azulene carboxaldehydes are likewise accessible by this route. *Arnold* and *Pahls* [36] synthetized 4,8-dimethylazulene-6-carboxaldehyde.

f) Stilbene-4-carboxaldehyde is obtained from 4-methylstilbene in an overall yield of ca. 65 % [37].

g) Fumardialdehyde dinitrone *(28)* is an interesting compound which can be synthetized in 87 % yield from butylene-1,4-bis(pyridinium bromide) *(27)* [38].

(27) *(28)*

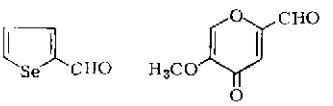
h) The dialdehyde *(29)*, which is obtainable *via* its bisnitrone, reacts with *o*-phenylenediamine to give the tetracyclic system *(30)* which contains an eight-membered ring; the yield is 75 % [39].



(29) *(30)*

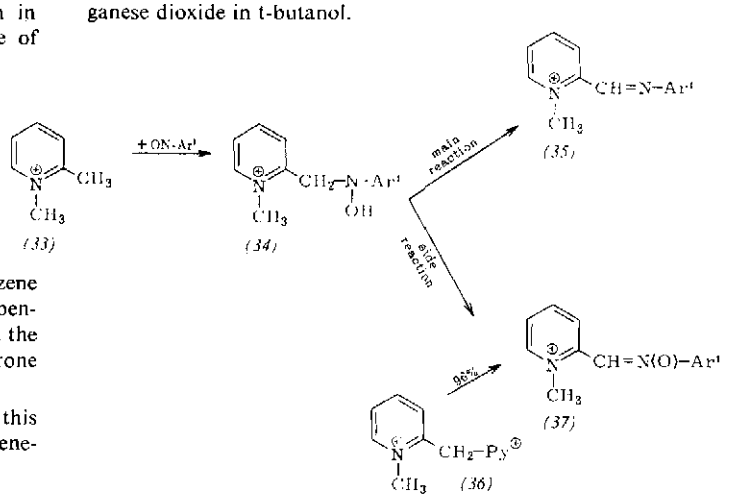
i) 2-Hydroxy-4-nitrotoluene yields the corresponding aldehyde. Reduction of its nitro group affords "PAS aldehyde" (2-hydroxy-4-aminobenzaldehyde) in 84 % yield, based on the pyridinium salt [40].

k) Selenophene-2-carboxaldehyde *(31)* is likewise produced in good yield from the corresponding methyl compound [41].



(31) *(32)*

l) 2-Formylcomene-*O*-methyl ether *(32)* is prepared from the 2-methyl compound [42]; however, it can also be obtained from the 2-hydroxymethyl derivative by oxidation with manganese dioxide in t-butanol.



m) The preparation of theobromine-8-carboxaldehyde (68 %) and theophylline-8-carboxaldehyde (23 %) from the methyl compounds [43] is better accomplished by the method of *Hull* [44], *viz.* by oxidation of the 8-hydroxymethylxanthines with sodium dichromate in glacial acetic acid;

[30] *K. Clarke*, J. chem. Soc. (London) *1957*, 3807.

[31] *W. Ried, H. Bodem, U. Ludwig*, and *N. Neidhardt*, Chem. Ber. *91*, 2479 (1958); see also *F. Kröhnke*, Ber. dtsch. chem. Ges. *71*, 2591 (1938).

[32] *M. C. Chaco* and *B. H. Jyger*, Current Sci. (India) *22*, 240 (1953); Chem. Abstr. *1954*, 2614c; J. org. Chemistry *25*, 186 (1960).

[33] *W. J. Leanza, J. P. Conbere, E. F. Rogers*, and *K. Pfister III*, J. Amer. chem. Soc. *76*, 1691 (1954); *K. Pfister III* and *W. J. Leanza*, US-Pat. 2708202 (May 10th, 1955); see *F. Kröhnke*, Angew. Chem. *65*, 614 (1953); *J. Fried* and *J. E. Herz*, US-Pat. 2920084 (Jan. 5th, 1960); US-Pat. 2972610 (Febr. 21st, 1961); *E. J. Agnello* and *G. D. Laubach*, Brit. Pat. 583884 (April 22nd, 1960); claims to 57 substances in the steroid-21-carboxaldehyde series, which were prepared either via nitrones or by oxidation of the corresponding alcohols with copper(II) acetate.

[34] *R. E. Beyler* and *F. Hoffmann*, J. Amer. chem. Soc. *79*, 5297 (1957); cf. *J. P. Conbere*, US-Pat. 2773077 (Dec. 4th, 1956).

[35] *W. Ried* and *Fr. J. Königstein*, Chem. Ber. *92*, 2532 (1959). It is probably easier to prepare the trialdehyde from trimesic acid.

[36] *F. Kröhnke*, Angew. Chem. *65*, 614 (1953); *H. Arnold* and *K. Pahls*, Chem. Ber. *87*, 257 (1954).

[37] *G. Drefahl* and *H. Lückert*, J. prakt. Chem. (4) *9*, 302 (1959).

[38] *O. Westphal* and *Kl. Jann*, Liebigs Ann. Chem. *605*, 9, 12 (1957).

[39] *G. Henseke* and *J. Müller*, Chem. Ber. *93*, 2668 (1960).

[40] *A. A. Goldberg* and *H. A. Walker*, J. chem. Soc. (London) *1954*, 2540.

[41] *Ju. K. Jurev, M. A. Gal'berstam*, and *N. K. Sadova*, Zh. obshch. Khim. *32*, 1301 (1962).

[42] *J. L. Looker* and *D. Shaneyfelt*, J. org. Chemistry *27*, 1894 (1962).

[43] *H. Bredereck, E. Siegel*, and *B. Fröhlisch*, Chem. Ber. *95*, 403 (1962).

[44] *R. Hull*, J. chem. Soc. (London) *1958*, 4069.

reaction according to the variant of *Giner-Sorolla* et al. [21] was evidently not tried in this case.

n) *Jaunin* and *Baer* [44a] obtained a satisfactory yield of ω,ω-di-(4-formylphenyl)polymethylenes from the corresponding chloromethyl derivatives.

Reaction of *p*-nitrosodimethylaniline with 2-picoline methiodide *(33)* [45] leads predominantly to the anil *(34)*, even if attempts are made to favor the formation of nitrone with an excess of nitrosoaryl compound; at a mole ratio of 1:1, 4% nitrone *(37)* and 96% anil *(35)* are obtained. Even with four molar equivalents of the nitrosoaryl reactant, the yield of nitrone is only 24%. The reason for this is that the pyridinium residue in *(34)* cannot be split off together with its pair of bonding electrons. Nitrone formation is possible here only by dehydration. In contrast, in the salt *(36)*, which can be prepared from α-picoline methiodide by the method of *Ortoleva* and *King* [46], the pyridine residue at the right-hand side of formula *(36)* separates easily and quantitatively; nitrone is obtained in 96% yield and free from anil.

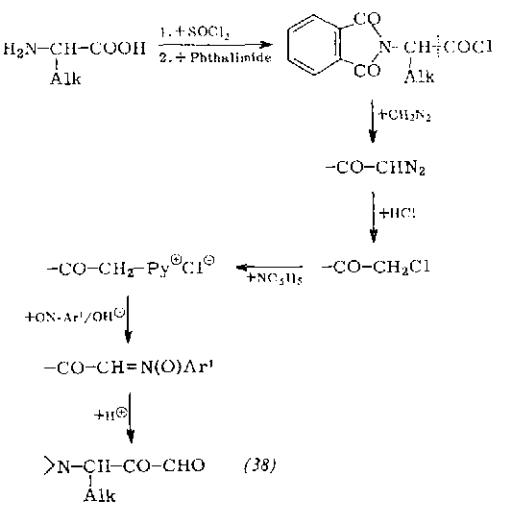
The relationships are very similar for the analogous γ-picolinium salts, except that here relatively more nitrone is obtained than in the α-series: The γ-position is somewhat more strongly positive, and a positive carbon atom close to the active methylene group generally promotes formation of nitrone [45,47].

3. Combinations with Other Methods

Combinations with other methods considerably extend the range of application of syntheses *via* nitrones.

a) *Combination with the Arndt-Eistert Method*

Synthesis of phthalimidopyruvaldehyde derivatives *(38)* is achieved by using an α-amino acid as the starting compound in conjunction with the chain-extending procedure of *Arndt* and *Eistert*.



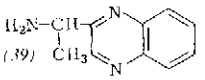
[44a] *R. Jaunin* and *T. Baer*, Helv. chim. Acta *41*, 104 (1958).

[45] *F. Kröhnke*, *H. Leister*, and *I. Vogt*, Chem. Ber. *90*, 2792 (1957).

[46] See *F. Kröhnke*, Angew. Chem. internat. Edit. *2*, 225 (1963).

[47] *H. Leister*, Ph.D. thesis, Universität Gießen, 1958, p. 48. It is also possible to obtain an anil-nitrone from bis(methylene) compounds, *e.g.* 1-indanone: *P. Pfeiffer* and *E. Milz*, Ber. dtsch. chem. Ges. *71*, 272 (1938).

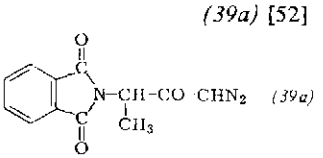
Removal of the phthalyl group by the method of *Ing* and *Manske* [48] yields aminopyruvaldehyde derivatives [49], which can be reduced very readily with H_2/PtO_2 to β-amino-α-hydroxypropaldehydes [50] and 3-aminopropane-1,2-diols [50,53]; with *o*-phenylenediamine, the



pyruvaldehyde derivatives give aminoalkylquinoxalines, *e.g. (39)* [51]. The aminopyruvaldehyde derivatives can be converted into their diethylacetals or bis(ethylenemercaptals) [49]. The corresponding acetals of phthalimido ethyl pyruvaldehyde were also prepared [50]. The mild conditions in all steps of the synthesis make it possible to achieve complete retention of configuration at an asymmetric carbon atom, as in L-alanine or L-tyrosine [49,52].

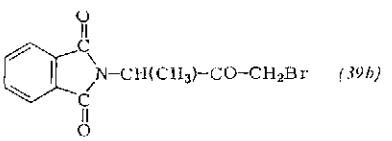
β-Amino-α-ketocarboxylic acids are produced in exactly the same way, using nitrosoaryl compounds and alkali cyanide (see Section III).

Preparation of (−)-1-Diazo-3-phthalimido-2-butanone (39a) [52]



A solution in ether (500 ml) of diazomethane prepared from 35 g of nitrosomethylurea is added to 6 g of *N*-phthaloyl-L-alanyl chloride [52] in 25 ml of benzene. After 24 hours, the mixture is filtered and the filtrate evaporated to dryness. The residue is dissolved in the minimum amount of dry ethyl acetate and reprecipitated with petroleum ether. The yield of *(39a)* is 5.2 g (85%); m.p. 88 °C; $\alpha_D^{18} = -69.3°$ (in ethyl acetate).

Preparation of (−)-1-Bromo-3-phthalimido-2-butanone (39b) [53]



A suspension of 5 g of 1-diazo-3-phthalimido-2-butanone in 27.5 ml of glacial acetic acid is stirred, and 5.3 ml of 48% hydrobromic acid are added. The mixture is allowed to stand for one hour at 20 °C and is then diluted with 300 ml of water. The yield of *(39b)* is 6 g (98%); m.p. 66 °C (from petroleum ether); $\alpha_D^{18} = -34.7°$ (in acetone).

[48] *H. R. Ing* and *R. H. F. Manske*, J. chem. Soc. (London) *1926*, 2348; improved procedure: *H. S. Mosher*, J. Amer. chem. Soc. *68*, 1565 (1946).

[49] *K. Balenović* and *N. Bregant*, J. org. Chemistry *17*, 1328 (1952).

[50] *K. Balenović*, *V. Skaric*, and *D. Dvornik*, Croatica Chemica Acta *28*, 231 (1956); Chem. Abstr. *51*, 11996c (1957).

[51] *J. Borkovec*, *J. Michalský*, *E. Rabušic*, and *J. Hadáček*, Chem. Listy svazek *48*, 717 (1954); Chem. Abstr. *1955*, 9662c; *J. Borkovec*, *J. Michalský*, and *M. Ambrož*, Chem. Listy svazek *48*, 865 (1954).

[52] *K. Balenović*, *D. Cerar*, and *Z. Fuks*, J. chem. Soc. (London) *1952*, 3316.

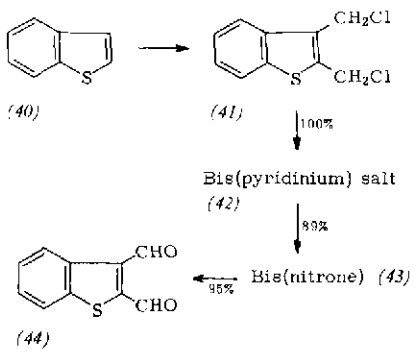
[53] *K. Balenović*, *D. Cerar*, and *L. Filipović*, J. org. Chemistry *18*, 868 (1953).

The hygroscopic pyridinium salt is obtained from the bromo compound in 98 % yield and melts at 85 °C (decomp.); $\alpha_D^{18} = -7.94°$ (in absolute ethanol) [53].

The nitrone [49], m.p. 153 °C, is formed in 50 % yield in the usual manner, as is the α-keto-aldehyde, (−)-α-phthalimidomethyl pyruvaldehyde [49]; the yield of aldehyde, based on the nitrone, is 80 %, $\alpha_D^{18} = -1.34 \pm 0.4°$ (in ether) [53].

b) *Combination with Chloromethylation*

Example 1 [54]: Thionaphthene-2,3-dicarboxaldehyde *(44)*, the first heterocyclic 2,3-dialdehyde, was synthetized from thionaphthene *(40)*. The overall yield over four steps was 42 %, based on the thionaphthene. Other routes were either not effective or unproductive.



Preparation of 2,3-Bis(chloromethyl)thionaphthene (41) [54]

A very rapid stream of dry hydrogen chloride is passed into a stirred suspension of 120 g (4 moles) of paraformaldehyde in 500 ml of glacial acetic acid. When solution of the paraformaldehyde is almost complete, 134 g (1 mole) of thionaphthene are added, and the mixture is kept at 60 °C for 6 to 8 hrs, the flow of HCl being reduced towards the end of this time. On standing overnight, *(41)* crystallizes out. Two extractions are made, each with 1500 ml of hot petroleum ether, from which compound *(41)* crystallizes out at −20 °C; m.p. after further recrystallization is 109–110 °C; the yield is 110–115 g (50 %).

2,3-Bis(pyridiniomethyl)thionaphthene dichloride *(42)* is obtained from *(41)* with excess pyridine at 100 °C. The yield is quantitative; m.p. 208–210 °C.

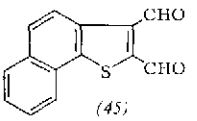
Preparation of the Bis(nitrone) (43)

A suspension of 3.89 g (0.01 mole) of *(42)* and 1 g of sodamide in 20 ml pyridine is prepared and 3 g (0.02 mole) of highly purified *p*-nitrosodimethylaniline and 5 ml of water are added very slowly at 20 to 30 °C with stirring, thus starting the reaction. After 12 hours, the mixture is cooled in ice and filtered; m.p. of *(43)* 200 °C, after recrystallization from dimethylformamide; the yield is 4 g (89 %).

Preparation of Thionaphthene-2,3-dicarboxaldehyde (44)

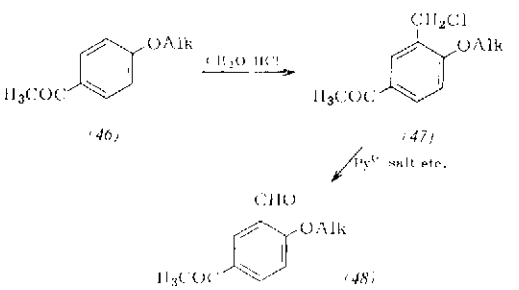
The bis(nitrone) *(43)* (9.16 g = 0.02 mole) is decomposed in a separatory funnel with 200–300 ml of 2 N HCl under 200 ml of ether. The reaction mixture is shaken for about 15 minutes and extracted three more times with 50 ml portions of ether; the ether extracts are combined, washed with water, and dried over sodium sulfate. The residue which is obtained on evaporation of the ether is of satisfactory purity for all reactions. The yield of *(44)* is 3.6 g (95 %); m.p. 111–112 °C, after recrystallization from ligroin of b.p. 80–100 °C.

Example 2: Chloromethylation of 6,7-benzothionaphthene gives 2,3-bis(chloromethyl)-6,7-benzothionaphthene (yield 89 %), from which 6,7-benzothionaphthene-2,3-dicarboxaldehyde *(45)* is obtained *via* the bis(pyridinium) salt (quantitative yield) and the bis(nitrone); the yield of *(45)* is 52 %, based on the bis(nitrone).



Compound *(45)* condenses with diethyl acetonedicarboxylate with formation of an additional seven-membered ring [55]. Starting from bis- and tris(bromomethyl)naphthalenes [56], the corresponding di- and triformylnaphthalenes were obtained in yields of 67–87 % and 57–86 %, respectively (based on the pyridinium salts) [57]. However, no two of the reacting groups may be *ortho* or *peri* to each other [57].

Example 3 [58]: Reaction of paraformaldehyde and hydrogen chloride with several *p*-alkoxyacetophenones *(46)* yielded 2-alkoxy-5-acetylbenzyl chlorides *(47)*. The corresponding aldehydes *(48)* were accessible only *via* the pyridinium salts; the yields lay between 51 and 64 %. It was unnecessary to isolate the nitrones.



c) *Combination with the Ortoleva-King Reaction*

The Ortoleva-King reaction refers to the direct reaction of active methyl and methylene compounds with iodine and pyridine to give pyridinium iodides [59]; thus, the first two steps in the formation of the pyridinium salts can be combined, generally with good yields (see also below).

$$\begin{matrix} R \\ R' \end{matrix}\!\!>\!CH_2 + I_2 + 2\,NC_5H_5 \longrightarrow \begin{matrix} R \\ R' \end{matrix}\!\!>\!CH\text{-}Py^{\oplus}I^{\ominus} + [Py^{\oplus}H]I^{\ominus}$$

As the reactions (a) to (d) indicate, methyl and methylene groups adjacent to a heterocyclic ring are especially suitable for the synthesis in combination with the Ortoleva-King reaction.

[54] *W. Ried* and *H. Bender*, Chem. Ber. *89*, 1574 (1956).

[55] *W. Ried* and *R. M. Gross*, Chem. Ber. *90*, 2646 (1957).

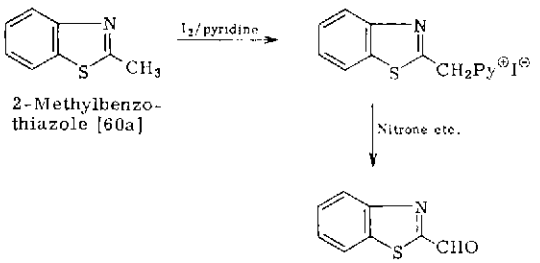
[56] *W. Ried* and *H. Bodem*, Chem. Ber. *91*, 1981 (1958).

[57] *W. Ried*, *H. Bodem*, *U. Ludwig*, and *H. Neidhardt*, Chem. Ber. *91*, 2479 (1958); see also [31].

[58] *E. Profft* and *R. Drux*, J. prakt. Chem. (4) *4*, 236 (1957).

[59] For further information and references, see *F. Kröhnke*, Angew. Chem. internat. Edit. *2*, 225 (1963); where further examples are given.

(a)

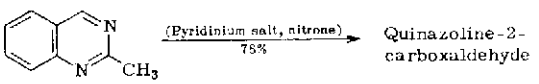


2-Methylbenzothiazole [60a]

Benzothiazole-2-carboxaldehyde (overall yield: 40%)

In an analogous manner, 2-methylnaphtho[1,2-*d*]thiazole is converted to β-naphthothiazole-2-carboxaldehyde [60a]. The nitrone derived from 2-methylbenzoxazole could not be cleaved [60a].

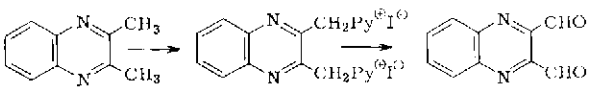
(b)



2-Methylquinazoline [60a]

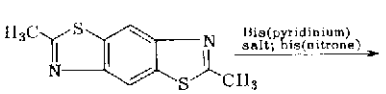
Similarly, the methyl groups in methylnaphthoxazoles, methylbenzoselenazoles, dimethylpyrimidines, and dimethylpyrazines can be converted to aldehyde groups. Only two methyl groups in tetramethylpyrazine react [60b].

(c)



Quinoxaline-2,3-dicarboxaldehyde [as its bis(phenylhydrazone)] [61]

(d)



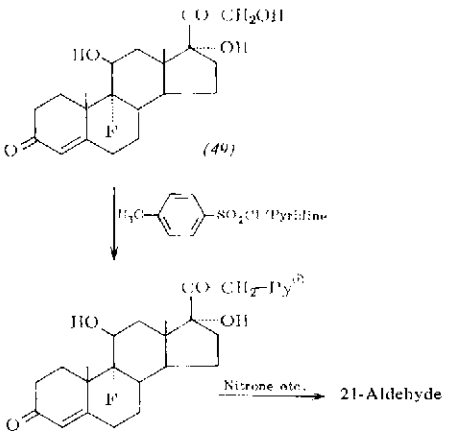
β-Benzobis(thiazole)-2,6-dicarboxaldehyde [60a] (overall yield 13.2%)

2,6-Dimethyl-β-benzobis(thiazole)

d) *P. Karrer's Variant*

By means of a variation introduced by *P. Karrer* [62], the bromomethyl compounds are replaced by the corresponding alcohols as the starting materials. The alcohols are first treated with *p*-toluenesulfonyl chloride and then with pyridine [63]. A recent example [64] is the reaction of 9α-fluorohydrocortisone *(49)* to yield the 21-aldehyde.

However, direct oxidation of the primary alcohol with sodium dichromate in glacial acetic acid by *Hull*'s method [44] also appears to be convenient.



4. Spontaneous Decomposition of Nitrones

Nitrones should normally be prepared at temperatures below 20 °C, and preferably at 0 °C [65], since they decompose in alkaline alcoholic solution; amides may be formed in the process. *α*-Keto-aldonitrones are transformed by the action of acetic anhydride or light into the isomeric amides [66].

$$RCH{=}N(O)Ar' \rightarrow RCO{-}NH{-}Ar'$$

Azomethines are formed in a regular fashion according to equations (e) to (h):

(e) $RCH{=}N(O)Ar' + H_2O \xrightarrow{[OH^\ominus]} RCHO + HN(OH)Ar'$

(f) $2HN(OH)Ar' \xrightarrow{\text{(Disprop.)}} ONAr' + H_2NAr' + H_2O$

(g) $H_2NAr' + RCHO \rightarrow RCH{=}NAr' + H_2O$

(h) $2\,RC(H{=}NO)Ar' \rightarrow RCH{=}NAr' + RCHO + ONAr'$

The corresponding azoxy compounds [66], nitrodimethylaniline, and other products are then obtained from the nitrosoaryl liberated in reaction (f). Nitrones may be separated readily from anils, since only the anil — which is more basic — is cleaved by alcoholic picric acid at 20 °C [67]. Nitrones may be recrystallized from alcohol, ethyl acetate, or especially well from dimethylformamide [68].

5. Syntheses with Nitrones

a) *Benzimidazoles*

α-Keto-aldonitrones are converted with *o*-phenylenediamine into quinoxalines [69]. With the same reagent

[60a] *W. Ried* and *H. Bender*, Chem. Ber. *89*, 1893 (1956).

[60b] *W. Ried* and *R. M. Gross*, Chem. Ber. *90*, 2646 (1957). In an analogous manner, 4-methyl- and 4-phenylthiazole-2-carboxaldehyde and naphtho[2,1-*d*]thiazole-2-carboxaldehyde are obtained from 2,4-dimethylthiazole, from 2-methyl-4-phenylthiazole, and from 2-methylnaphtho[2,1-*d*]thiazole, respectively: *T. Uno* and *S. Akihamo*, J. pharm. Soc. Japan *81*, 579 (1961).

[61] *G. Henseke* and *Kl.-J. Bähner*, Chem. Ber. *91*, 1605 (1958); see, however, *N. Schulze*, J. prakt. Chem. (4) *19*, 214, 215, 221 (1963).

[62] *P. Karrer* and *A. Epprecht*, Helv. chim. Acta *24*, 1039 (1941).

[63] See *F. Kröhnke*, Angew. Chem. *65*, 613 (1953), right-hand column.

[64] *J. Fried* and *J. E. Herz*, US-Pat. 2972610 (Febr. 21st, 1961).

[65] *F. Kröhnke*, *H. Leister*, and *I. Vogt*, Chem. Ber. *90*, 2792 (1957), particularly pp. 2796 et seq.

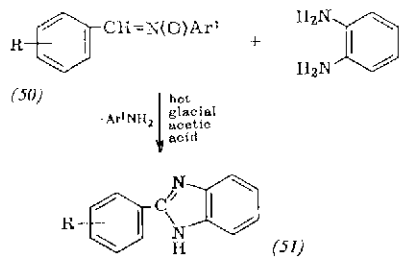
[66] *F. Kröhnke*, Liebigs Ann. Chem. *604*, 203 (1957); it is shown there that the rearrangement of nitrones to amides should not be interpreted as a Beckmann rearrangement; *E. Schmitz*, Chem. Ber. *91*, 1488 (1958); *B. Umezawa*, Chem. pharmac. Bull. (Tokyo) *8*, 698, 967 (1960).

[67] In *F. Kröhnke*, Angew. Chem. *65*, 613 (1953), top of left-hand column, it is stated, "nitrones are cleaved by acids as easily as Schiff bases are". This statement must be corrected: the anil is cleaved so much more easily that it can thus be separated from the nitrone: *F. Kröhnke*, *H. Leister*, and *I. Vogt*, Chem. Ber. *90*, 2795 (1957).

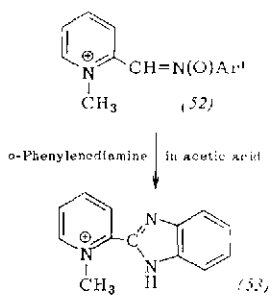
[68] *W. Ried* and *H. Bender*, Chem. Ber. *89*, 1576 (1956).

[69] *F. Kröhnke*, Chem. Ber. *80*, 300 (1947); Angew. Chem. *65*, 616 (1953).

in hot glacial acetic acid, benzaldehyde nitrones *(50)* give benzimidazoles *(51)* in quantitative yields [70]; no reaction occurs in hot alcohol or in dimethylformamide.

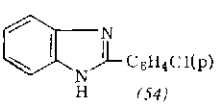


The dehydrogenation required for the formation of *(51)* is evidently achieved with the oxygen of the nitrone. Benzimidazoles may also be synthetized directly from the corresponding benzylpyridinium salts, which are transformed by known means into the nitrones, which are then boiled with *o*-phenylenediamine in glacial acetic acid without isolation. Thus, *N*-methyl-2-(benzimidazol-2-yl)pyridinium iodide *(53)* is obtained from the *p*-dimethylaminophenylnitrone of *N*-methylpyridinium-2-carboxaldehyde iodide *(52)* [71].



Preparation of 2-(p-Chlorophenyl)benzimidazole (54)

One mmole of *p*-chlorobenzylpyridinium bromide and 1 mmole of *p*-nitrosodimethylaniline in 90 % alcohol are transformed to the nitrone at 0 °C with 1 ml of 1 N sodium hydroxide. After standing for 1 hour, the mixture is treated



with a solution of 1.5 mmole of *o*-phenylenediamine in 10 ml of glacial acetic acid and heated for about 15 minutes. The benzimidazole (yield 79 %) is precipitated with water, sometimes after preliminary concentration *in vacuo*; colorless needles, m.p. 293 °C, from 90 parts of ethyl acetate.

b) *Benzothiazoles*

In corresponding fashion, *o*-aminothiophenol reacts with benzylpyridinium salts to form the expected benzothiazoles in very good yields *via* the intermediate benzaldehyde nitrones [72].

[70] *F. Kröhnke* and *H. Leister*, Chem. Ber. *91*, 1479, 1484, 1487 (1958).

[71] *H. Leister*, Ph. D. thesis, Universität Gießen, 1958, pp. 53, 79; see also [72].

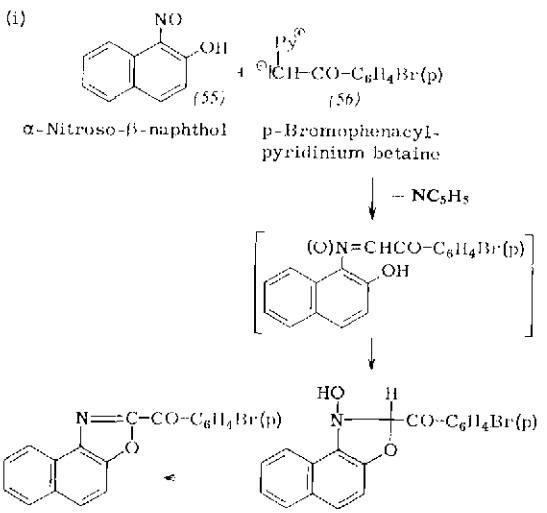
[72] *F. Kröhnke* and *H. Leister*, Chem. Ber. *91*, 1479 (1958).

Preparation of 2-(m-Nitrophenyl)benzothiazole [72]

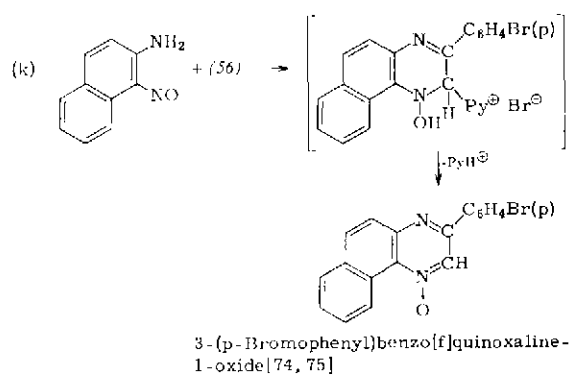
As in the preceding example 1 mmole of *m*-nitrobenzylpyridinium bromide is transformed to the nitrone, which is heated in the same manner with 1.5 mmole of *o*-aminothiophenol in acetic acid for 15 min. On addition of water, an almost quantitative yield of colorless needles is obtained; m.p. 185 186 °C after recrystallization from 35 parts of ethyl acetate [73].

6. New Ring Systems from Amino- and Hydroxy-nitrosoaromatics

New reactions of aromatic nitroso compounds with pyridinium salts containing active methylene groups are outlined in equations (i) to (l); these reactions proceed



by elimination of pyridine and lead to the naphthoxazole, benzoquinoxaline, and thionaphthoxazone ring systems.



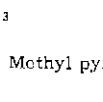
The corresponding *N(4)*-oxide is formed from β-nitroso-α-naphthylamine [74, 75].

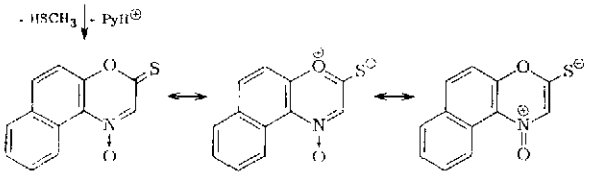
[73] Beilsteins Handbuch der organischen Chemie, 4th Ed. Springer, Heidelberg, Vol. 27, p. 38; *M. T. Bogert* and *H. B. Corbitt*, J. Amer. chem. Soc. *48*, 785 (1926).

[74] *Kl. Gerlach* and *F. Kröhnke*, Chem. Ber. *95*, 1124 (1962); *Kl. Gerlach*, Ph. D. thesis, Universität Gießen, 1960, p. 21.

[75] *A. M. Patterson, L. T. Capell*, and *D. F. Walker:* The Ring Index. 2nd Ed., American Chemical Society, Washington 1959, p. 439, No. 3393.

(1)

(55) +  Methyl pyridiniodithioacetate iodide

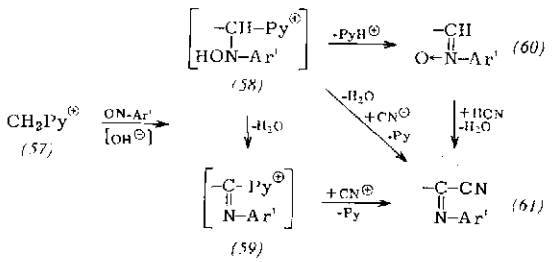


3-Thionaphth[2,1-b]-[1,4]oxazin-3-one-1-oxide [74]

III. Syntheses via α-Cyanoanils

(Including Nucleophilic Exchange Reactions Involving Pyridinium Salts)

The reaction with *p*-nitrosodimethylaniline/sodium cyanide leading to α-cyanoanils, which is associated with a change in color to red, appears to be one of the commonest indications of active methylene groups. The reaction does not necessarily proceed *via* nitrones *(60)*, but in the main *via* a common, aldol-like intermediate *(58)* [76, 77].

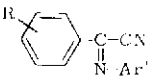


S_N2 reaction of the cyanide ion with *(58)* or *(59)* displaces the pyridinium cation as pyridine, *i.e.* together with the bonding electron pair. Thus, pyridinium salts *(57)* as well as benzyl and phenacyl halides [76] give better yields of α-cyanoanils *(61)* than of nitrones *(60)* [78].

It appears from this fact that α-cyanoanils are even more suitable for syntheses of α-ketocarboxylic acids than nitrones are for syntheses of aldehydes or α-ketoaldehydes. In addition, a phenacyltrimethylammonium salt, for example, gives virtually no reaction with nitrosoaryl/sodium hydroxide solution at 20 °C, but with nitrosodimethylaniline/sodium cyanide, it yields "red anil" in 40 % yield [79]. Moreover, α-cyanoanils, but not nitrones, can be obtained from phenyl phenacyl ethers [77].

1. *p*-Dimethylaminoanils of Benzoyl Cyanides

It has been shown that the synthesis of *p*-dimethylaminoanils of benzoyl cyanides *(62)* is simpler and better if it starts directly from benzyl halides rather than from pyridinium salts, provided the phenyl nucleus carries a substituent imparting a (−I)-effect [76]. Alternatively,



(62)

the halide is first converted to the nitrile, which is then treated with the nitrosoaryl reagent [80]. This is one of the rare cases in which the detour *via* the pyridinium salt is not rewarding, and is unadvisable.

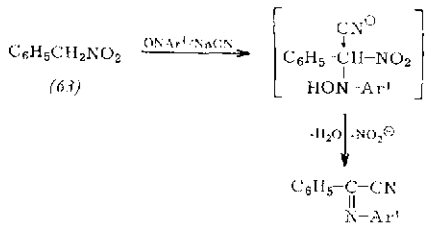
Preparation of 2,4-Dichlorobenzoyl Cyanide p-Dimethylaminoanil (62); R = 2,4-dichloro- [81]

A solution of 2,4-dichlorobenzyl bromide (0.48 g or 2 mmoles) in 12 ml of ethanol is treated at 20 °C with a solution of 3 mmoles of *p*-nitrosodimethylaniline in 5 ml of acetone, then with 0.3 g of pure potassium cyanide in 2 ml of water. After 2 hours, 15 ml of water are added, and the mixture is allowed to stand for some time at 0 °C. The yield of *(62)* is 550 mg (86.5 %). Yellow, matted needles first appear from ethyl acetate, and are soon transformed to red rhombohedra with a green metallic lustre; m.p. 129 °C.

The yield is smaller if the starting material is 2,4-dichlorobenzylpyridinium bromide. The nitrone obtained from this salt with nitrosodimethylaniline/sodium hydroxide was converted, with sodium cyanide in alcohol, to the anil *(62)* in 74 % yield. *o*-Chlorobenzoyl cyanide *p*-dimethylaminoanil (m.p. 79–80 °C) was formed analogously from *o*-chlorobenzyl bromide in 56 % yield [81, 82]. The yield is even better (75 %) if the *o*-chlorobenzyl bromide is first converted to *o*-chlorobenzyl cyanide (which need not be isolated) by boiling with sodium cyanide in aqueous alcohol [80].

Such cyanoanils are converted quantitatively to carboxylic acids by hot mineral acids; hydrogen cyanide and *p*-dimethylaminoaniline are eliminated in the process. Thus, toluenes and benzyl halides – or their pyridinium salts – can be satisfactorily converted to benzoic acids, *etc.* [83].

The α-cyanoanil of formula *(62)*, R = H, is also accessible from phenylnitromethane *(63)* in a yield of 82.4 % [84].



(63)

In this reaction the NO_2 residue is displaced as the nitrite anion by the $CN^{\ominus}$.

[76] *F. Kröhnke* and *G. Kröhnke*, Chem. Ber. *91*, 1474 (1958).

[77] *F. Kröhnke*, *G. Kröhnke*, and *G. M. Ahrenholz*, J. prakt. Chem. (4) *11*, 239, 242 (1960).

[78] This does not preclude the possibility that α-cyanoanils may sometimes be prepared conveniently from nitrones.

[79] *F. Kröhnke*, Chem. Ber. *80*, 298 (1947).

[80] See *H. H. Steuernagel*, Diploma thesis, Universität Gießen, 1959, p. 43. Dimethylformamide is suitable as solvent for the conversion of halides to nitriles. *W. Schulze*, J. prakt. Chem. (4) *19*, 93 (1963).

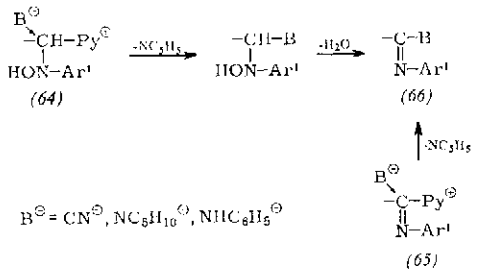
[81] *A. Peuser*, Diploma thesis, Universität Gießen, 1960, p. 31.

[82] The data of *F. Kröhnke* and *G. Kröhnke*, Chem. Ber. *91*, 1478 (1958) in No. 1 of Table 1 ["Pure yield according to preparative method a)"] should therefore be corrected.

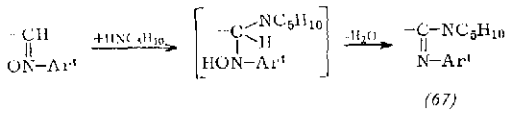
[83] See *F. Kröhnke*, Angew. Chem. *65*, 615 (1953), right-hand column.

[84] *H. H. Steuernagel*, Diploma thesis, Universität Gießen, 1959, pp. 31, 50; *F. Kröhnke* and *H. H. Steuernagel*, Chem. Ber. *96*, 494 (1963).

Instead of the cyanide anion, hot aqueous piperidine or aniline can also be used to displace the pyridine from the groups *(64)* and *(65)*; the product is then an *N,N'*-disubstituted amidine containing the grouping *(66)* [85]. Here the effective reagent is the anion $NC_5H_{10}^{\ominus}$ or $NHC_6H_5^{\ominus}$.

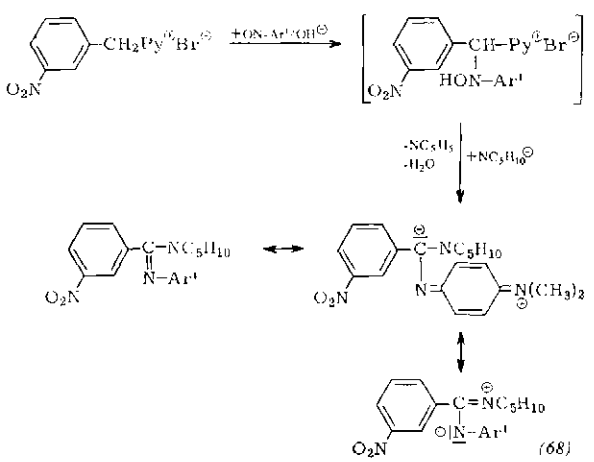


Just as for the cyanoanils, the amidines *(67)* obtained with piperidine can also be prepared from the nitrones [85].



Thus, here too, as in the case of the cyanoanils, the nitrones are possible but not essential intermediates; the yields of amidines from nitrones are not good, because the nitrones are converted with hot piperidine to azomethines, and amides may also occur [86]. It is therefore preferable to start the preparation of an amidine containing the group *(66)*, B = NC_5H_{10}, from the pyridinium salt and to make the amidine in a single operation.

Preparation of N,N-Cyclopentamethylene-N'-(4-dimethylaminophenyl)-3-nitrobenzamidine (68) [85]

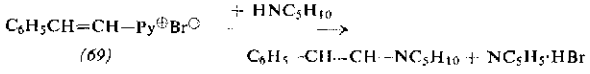


One mmole of *m*-nitrobenzylpyridinium bromide is heated on a steam bath for 15 minutes with 1 mmole of nitrosodimethylaniline in 6 ml of piperidine and 3 ml of water. The mixture is evaporated *in vacuo*, the residue taken up in some methanol, and the hydroperchlorate carefully precipitated with 1 N perchloric acid. The yield of hydroperchlorate of *(68)* is 52 %; yellow-red needles, m.p. 169 °C after recrystallization from ethanol. The free base resulting from treatment with 2 N sodium hydroxide crystallizes from ethanol as red needles, m.p. 122–123 °C. The yield of base from the nitrone amounted to only 10 %, along with 37 % of the Schiff base *N*-(3-nitrobenzylidene)-4-dimethylaminoaniline.

[85] *I. Vogt, F. Kröhnke*, and *W. Fischer*, unpublished results.

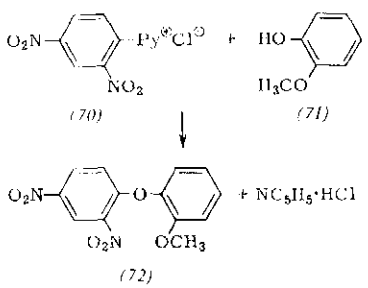
[86] See, for example, *F. Kröhnke*, Liebigs Ann. Chem. *604*, 203 (1957).

The *N*-alkylation of piperidine which occurs on heating it with styrylpyridinium bromide *(69)* and which yields *N*-styrylpiperidine [87] can be interpreted in the same way.

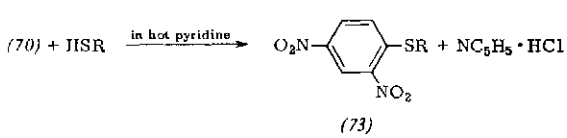


With other substrates, hot aqueous piperidine causes cleavage of the pyridinium ring with formation of enamines, which are then converted smoothly by acids to (substituted) deoxybenzoins [88].

Nucleophilic displacement of pyridine in pyridinium salts by an S_N2 reaction is rather common. Secondary [89] and primary amines (aniline) [90] can accomplish this. According to *Bielig* and *Reidies* [92], the conversion of 2,4-dinitrophenylpyridinium chloride *(70)* with aniline hydrochloride to dinitrodiphenylamine or with guaiacol



(71) to the substituted diphenyl ether *(72)* [91] has wider application, being also of preparative value in the synthesis of unsymmetrical thioethers *(73)*.



These authors discovered the equilibrium relationships which exist between the formation of ethers from pyridinium salts and their cleavage by these salts, *e.g.* by the method of *Prey* [93]. Such exchange reactions require sufficient nucleophilicity in the moiety which displaces the pyridinium residue, and as strong a (−I)-effect as possible in the substituent at the pyridinium nitrogen. It is well known that the pyridine in acylpyridinium salts is easily displaced even by hydroxyl ion.

[87] *F. Kröhnke* and *I. Vogt*, Liebigs Ann. Chem. *589*, 52 (1954).

[88] *F. Kröhnke* and *I. Vogt*, Liebigs Ann. Chem. *589*, 26 (1954); *F. Kröhnke*, Angew. Chem. *65*, 620 (1953), top of left-hand column.

[89] *A. J. Birch*, J. chem. Soc. (London) *1944*, 314; see *F. Kröhnke*, Angew. Chem. *65*, 625 (1953), middle of left-hand column.

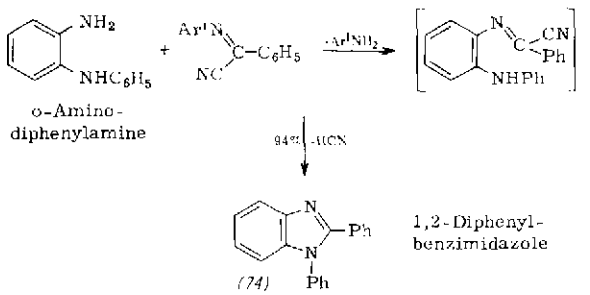
[90] *A. F. Vompe* and *N. F. Turitsyna*, Dokl. Akad. Nauk SSSR *64*, 341 (1949); Chem. Abstr. *43*, 4671 (1949).

[91] *F. Kröhnke*, Angew. Chem. *65*, 624 (1953), top of right-hand column.

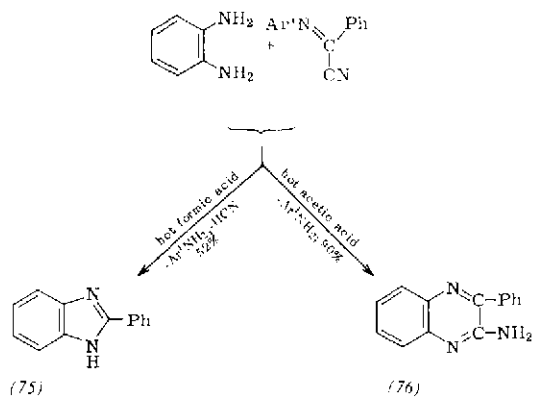
[92] *H.-J. Bielig* and *A. Reidies*, Chem. Ber. *89*, 550 (1956); see also *Th. Zincke* and *G. Weißpfennig*, J. prakt. Chem. (2) *85*, 211 (1912); *E. T. Borrows, J. C. Clayton, B. A. Hems* and *A. G. Long*, J. chem. Soc. (London) *1949*, Part V, 190 (preparation of diaryl ethers by this method).

[93] *V. Prey*, Ber. dtsch. chem. Ges. *74*, 1219 (1941); *75*, 350, 445, 537 (1942).

Sachs and *Bry* [94] were the first to show that aniline can also displace the cyano residue from α-cyanoanils. This opens a route leading to amidines that is capable of further extension [95]. In addition, it is possible to obtain benzimidazoles *(74)* very smoothly by intramolecular displacement of the cyano by an anilino



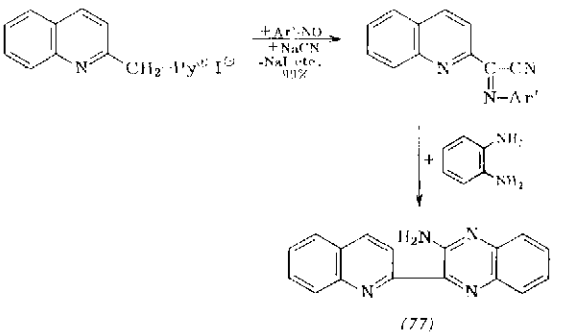
group [96]. If *o*-phenylenediamine is the starting material, benzimidazole *(75)* is formed in hot formic acid [97], whereas in hot acetic acid the product is a quinoxaline *(76)* [96].



Thus, 2-aminoquinoxalines of type *(76)* can be prepared directly from pyridinium salts.

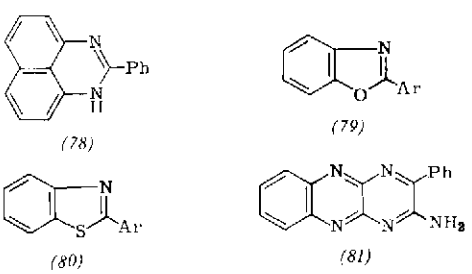
Preparation of 2-Amino-3-quinol-2-ylquinoxaline (77)

A solution of 1.045 g (3 mmoles) of 1-quinol-2-ylmethylpyridinium iodide [98, 99] in 12 ml of 50 % ethanol is cooled to 20 °C and added to a mixture of 0.5 g of *p*-nitrosodimethylaniline in 12 ml of ethanol and 0.3 g of sodium cyanide in 2 ml of water. The green solution becomes deep red at once, and soon solidifies to a mass of dark red crystals of the cyanoanil. After addition of an equal volume of water, the mixture is allowed to stand for 30 min at 0 °C; the precipitate is filtered and washed with cold water. After recrystallization from 20 parts of ethyl acetate, carmine-red prisms of quinol-2-ylglyoxylonitrile *p*-dimethylaminoanil are obtained, m.p. 157–158 °C; the yield is 0.9 g (99 %) [100]. This compound (300 mg, 1 mmole) is dissolved in 2.5 ml of glacial acetic acid and the solution boiled briefly with 0.2 g of *o*-phenylenediamine in 3 ml of 50 % acetic acid and allowed to heat for 30 min on a steam bath. After a transitory blue coloration, the solution becomes deep brown. Water is



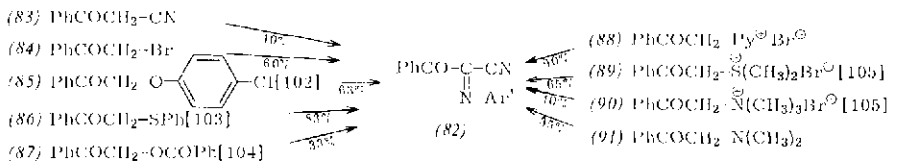
added, and crystallization is completed at 0 °C. The yield is 260 mg (95 %). Recrystallization from 100 parts of ethanol (with animal charcoal) gives small yellow needles of *(77)*, m.p. 215.5–217 °C.

By replacing the *o*-phenylenediamine with 1,8-naphthylenediamine, analogous perimidines such as *(78)* [96] are obtained, while *o*-aminophenols give benzoxazoles *(79)* [96], *o*-aminothiophenols give benzothiazoles *(80)* [96], and 2,3-diaminoquinoxaline gives, although with much greater difficulty, 2-amino-3-phenyl-1,4,9,10-tetra-aza-anthracene *(81)* [101].



2. Benzoylglyoxylonitrile *p*-Dimethylaminoanils

The manifold possibilities for the preparation of benzoylglyoxylonitrile *p*-dimethylaminoanil *(82)*, and hence



Scheme 1. Possible modes of formation of benzoylglyoxylonitrile *p*-dimethylaminoanils *(82)*.

the ease of formation of "red anils", are shown in Scheme 1. The "red anil" *(82)* is formed by treatment of

[94] *F. Sachs* and *E. Bry*, Ber. dtsch. chem. Ges. *34*, 118 (1901).

[95] *F. Kröhnke* and *H. H. Steuernagel*, Chem. Ber. *96*, 486 (1963); Concerning the formation of quinoxalines from α-keto-aldonitrones, see *F. Kröhnke*, Chem. Ber. *80*, 300 (1947); Angew. Chem. *65*, 616 (1953) top of right-hand column.

[96] *F. Kröhnke* and *H. Leister*, Chem. Ber. *91*, 1479 (1958).

[97] *H. Leister*, Ph.D. thesis, Universität Gießen, 1958, p. 14. Probably the stronger acid formic acid converts the anil $Ar'N-C(CN)C_6H_5$ to benzoic acid which reacts with the *o*-phenylenediamine to give the benzimidazole *(75)*.

[98] *F. Kröhnke* and *K. F. Groß*, Chem. Ber. *92*, 29, 30 (1959).

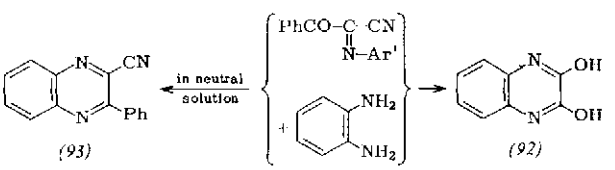
[99] *L. C. King*, J. Amer. chem. Soc. *66*, 894 (1944).

[100] *W. Borsche* and *R. Manteufel*, Liebigs Ann. Chem. *526*, 22 (1936); preparation from quinolylacetonitrile with nitrosodimethylaniline.

[101] *A. Peuser*, Diploma thesis, Universität Gießen, 1960, pp. 22, 39; cf. *O. Hinsberg* and *E. Schwantes*, Ber. dtsch. chem. Ges. *36*, 4039 (1903).

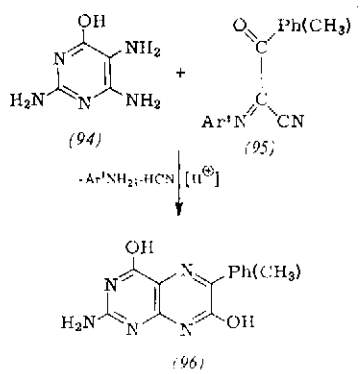
alcoholic solutions of the phenacyl compounds *(84)* to *(91)* with nitrosodimethylaniline/sodium cyanide, or of compound *(83)* with nitrosodimethylaniline/sodium hydroxide.

If the "red anils", which are most suitably obtained from phenacylpyridinium bromide, are treated with *o*-phenylenediamine in the presence of mineral acids, 3-hydroxyquinoxalines *(92)* are obtained; in neutral solution, the reaction leads to 3-cyanoquinoxalines *(93)* [106].



(93) *(92)*

In the synthesis of a xanthopterine, *viz.* 6-hydroxy-2,4,5-triaminopyrimidine *(95)*, from *(94)*, *Korte* [107] made use of this possibility of obtaining quinoxalines.



(94) *(95)* *(96)*

Phenyl-(or methyl-)isoxanthopterine together with phenyl-(or methyl-)xanthopterine

[102] *F. Kröhnke, G. Kröhnke,* and *G. M. Ahrenholz,* J. prakt. Chem. (4) *11*, 239, 242, 247 (1960).

[103] *F. Kröhnke, G. M. Ahrenholz,* and *K. F. Groß,* J. prakt. Chem. (4) *11*, 256 (1960).

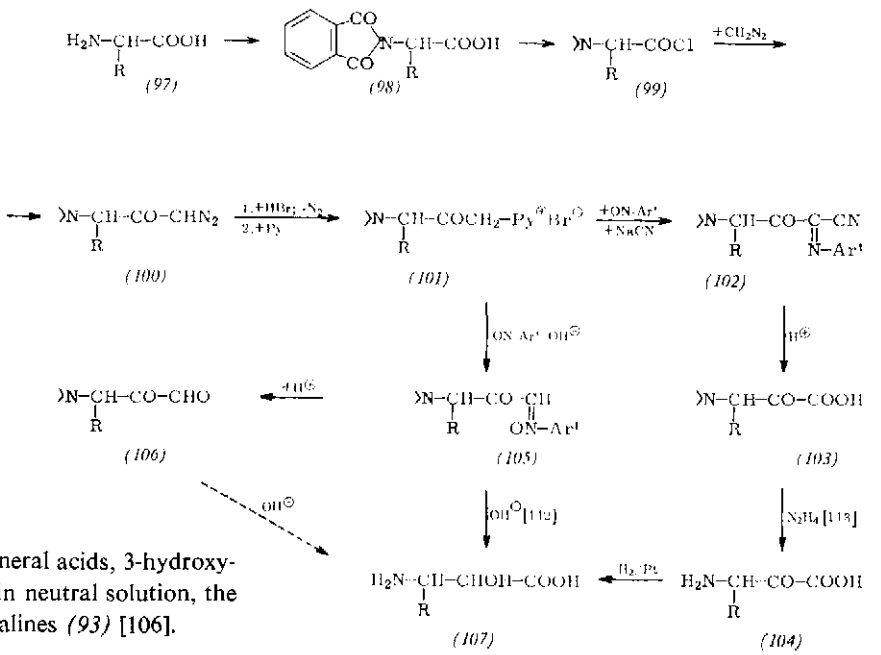
[104] *K. Ellegast,* cited in *F. Kröhnke* and *G. Kröhnke,* Chem. Ber. *91*, 1476 (1958).

[105] *F. Kröhnke,* footnote [79]; *A. Chlopczik,* Diploma thesis, Universität Gießen, 1961, pp. 14, 30.

[106] *F. Kröhnke,* Chem. Ber. *80*, 300, 309 (1947); *J. Borkovec, J. Michalský* and *A. Podpěrová,* Chem. Listy Svazek *49*, 1405(1955).

[107] *F. Korte,* Chem. Ber. *85*, 1018 (1952).

α-Cyanoanils have found numerous useful synthetic applications in recent years, principally in the preparation of otherwise almost inaccessible compounds such as α-keto-carboxylic acids [108] and aminoketo- and



aminohydroxy-carboxylic acids. In particular, the research groups of *Balenović* [109] in Zagreb (Yugoslavia), and of *Michalský* and *Borkovec* [110] in Brno (Czechoslovakia), obtained α-keto-ω-aminocarboxylic acids *(104)* in a smooth reaction from amino acids *(97)* when the amino group was protected by means of the phthaloyl group *(98)*; the α-keto-ω-aminocarboxylic acids yielded the corresponding quinoxalines. In the simplest case, α-keto-β-aminopropionic acid is obtained from glycine:

$$H_2N{-}CH_2{-}COOH \rightarrow H_2N{-}CH_2{-}CO{-}COOH$$

Here, as in the other examples, the method of obtaining α-cyanoanils *(102)* was combined with the *Arndt-Eistert* method in order to synthetize homologous carboxylic acids [111].

The phthaloyl group in *(103)* was removed at the conclusion of the synthesis using alcoholic hydrazine hydrate *(104)* according to the method of *Ing* and *Manske* [113]. Thus, β-alanine, DL-valine, DL-α-aminobutyric acid, and other amino acids, including those with branched alkyl chains, are accessible by this combined synthetic procedure; *e.g.* α-keto-γ-aminocapric acid *(108)* is obtainable from 6-amino-nonanoic acid [114].

[108] *F. Kröhnke,* Chem. Ber. *80*, 310 (1947).

[109] *K. Balenović, D. Cerar,* and *N. Bregant,* Croatica Chemica Acta *28*, 279 (1956).

[110] Review: *J. Michalský,* J. prakt. Chem. (4) *8*, 186 (1959).

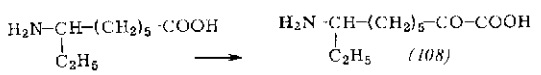
[111] Cf. Chapter III, Section 3a.

[112] Cf. *G. Sanna,* Gazz. chim. ital. *78*, 742 (1948).

[113] *H. R. Ing* and *R. H. F. Manske,* J. chem. Soc. (London) *1926*, 2348; *H. S. Mosher,* J. Amer. chem. Soc. *68*, 1565 (1946).

[114] *J. Michalský,* J. prakt. Chem. (4) *8*, 189 (1959).

It is possible to conduct all operations under such mild conditions, in particular by working at sufficiently low temperatures, that the configuration of the H_2N-C(R)H-group remains unchanged [115], just as in the similar

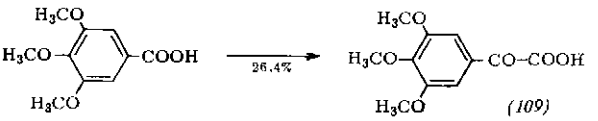


(108)

synthesis of the aminopyruvaldehyde derivatives *(101)* → *(105)* → *(106)* [115] (see also Section II.3a); no racemization or Walden inversion occurs. α-Hydroxy-ω-aminocarboxylic acids *(107)* are also accessible in this way from *(104)*, *(105)*, or *(106)*.

By condensing the α-keto-δ-aminovaleric acid obtained in this manner with *o*-aminobenzaldehyde, *Macholán* [116] was able to synthetize deoxyvasicine, in analogy to the synthesis developed by *Schöpf* [117] starting from γ-aminobutyraldehyde and *o*-aminobenzaldehyde.

In the first communication of this series [118], additional preparative applications proceeding by way of α-cyanoanils were discussed. In conjunction with the *Arndt-Eistert* reaction, 3,4,5-trimethoxyphenylglyoxylic acid *(109)* can be synthetized, for example [119].



(109)

The intermediate 3,4,5-trimethoxy-ω-chloroacetophenone is formed in 40 % yield by the *Arndt-Eistert* method. From this, the final product is obtained in 66 % yield; the overall yield thus amounts to 26.4 %.

IV. Erratum

In Communication No. II, Angew. Chem. internat. Edit. *1*, 626 (1962), page 630, left-hand column, line 16, read: 3-(benzylideneacetyl)pyridine.

Cordial thanks are due to Frau Lotte Gürich for her valuable aid in the composition of the manuscripts of the second, third, and fourth communications.

Received March 13th, 1962; extended version received January 31st, 1963 [A 286/97 IE]
German version: Angew. Chem. *75*, 317 (1963).

[115] *K. Balenović, D. Cerar*, and *N. Bregant*, Croatica Chemica Acta *28*, 279 (1956); Chem. Abstr. *1957*, 12000e.

[116] *L. Macholán*, Chem. Listy svazek *51*, 2122 (1957).

[117] *C. Schöpf* and *F. Oechsler*, Liebigs Ann. Chem. *523*, 1 (1936).

[118] *F. Kröhnke*, Angew. Chem. *65*, 615 (1953).

[119] *J. Michalkský* and *L. Sadílek*, Mh. Chem. *90*, 171 (1959); see also *J. Michalský* and *M. Smrz*, ibid. *91*, 307 (1960).

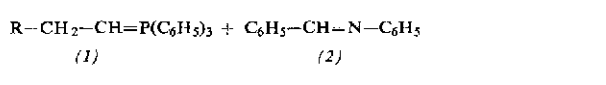
COMMUNICATIONS

Reaction of Alkylenetriphenylphosphoranes with Schiff Bases

By Priv. Doz. Dr. H. J. Bestmann and Dipl.-Chem. F. Seng

Institut für Organische Chemie der Technischen Hochschule München (Germany)

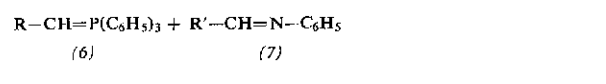
Alkylenetriphenylphosphoranes *(1)* containing a CH_2 group in the β-position to the phosphorus atom react at 130 to 150 °C with benzylideneaniline *(2)* as follows:



a) R = H b) R = C_3H_7

Ethylenetriphenylphosphorane *(1a)* and *(2)* gave phenylallene *(3a)* in 62 % yield and triphenylphosphine *(4)* in 60 % yield accompanied by aniline *(5)* in 56 % yield. In an analogous manner, butylenetriphenylphosphorane *(1b)* gives 1-phenyl-3-propylallene *(3b)* in 46 % yield which, according to its infrared spectrum, is contaminated by the isomeric acetylene derivative.

Alkylenephosphoranes with no CH_2 group in the β-position to the phosphorus atom *(6)* react at 150–180 °C with Schiff bases *(7)* analogous to a Wittig reaction to give olefins *(8)* and phenyliminotriphenylphosphorane *(9)*:



Olefins prepared from alkylene phosphoranes and Schiff bases

R	R′	*(8)*	Yield [%]
C_6H_5	C_6H_5	stilbene	50
C_6H_5	C_6H_5–CH=CH	1,4-diphenylbutadiene	68
C_6H_5–CH=CH	C_6H_5	1,4-diphenylbutadiene	68

Received, January 17th, 1963 [Z 484/323 IE]
Publication withheld until now at the request of the authors.
German version: Angew. Chem. *75*, 475 (1963).

$BaSi_2$, a Phase with Discrete Si_4 Tetrahedra

By Dr. Herbert Schäfer, cand. chem. K. H. Janzon, and Prof. Dr. Armin Weiss

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$BaSi_2$, which was first prepared by *Wöhler* and *Schuff* [1] from BaSi and Si, is obtained in the form of analytically pure rhombic-dipyramidal single crystals when stoichiometric proportions of Ba and Si are melted at 1150 °C in an inert-gas atmosphere and then cooled slowly (Ba found 70.4 %, calc. 70.9 %; Si found 28.0 %, calc. 29.1 %).

In contrast to SrSi [2] and BaSi [3], which are isotypic with CaSi [4], the Si atoms in $BaSi_2$ do not form layers as in $CaSi_2$ [5], but form discrete Si_4 tetrahedra. The Si–Si distances within each tetrahedron are 2.34 Å, 2.37 Å, 2.37 Å, 2.41 Å, 2.48 Å, and 2.48 Å. The $\diagdown\overset{Si}{}\diagup$ bond angles are between 57 ° and 62 °. The distances within a tetrahedron are of the same magnitude as those in elemental Si (2.34 Å), in the $\diagdown\overset{Si}{}\diagup$ chains of CaSi (2.47 Å), SrSi (2.52 Å), BaSi (2.52 Å), or in the

layers of $CaSi_2$ (2.48 Å). A homopolar bond is therefore indicated. The shortest Ba–Si distance is 3.39 Å, the Ba–Ba distances are 4.38 Å and 4.44 Å. The shortest Si–Si distance between tetrahedra is 4.03 Å – substantially longer than the distances within the tetrahedron.

If $BaSi_2$ were largely ionogenic with Ba^{2+} and Si^- ions, then it would be plausible for the Si^- ions to form tetrahedra, just like phosphorus with which they are isoelectronic.

In contrast to Ba_2Si and BaSi, $BaSi_2$ is relatively stable towards air. It decomposes rapidly in acids; no spontaneously inflammable silanes are formed, however.

Crystallographic data for $BaSi_2$:

orthorhombic – a = 8.92 Å, b = 6.80 Å, c = 11.58 Å

$d_{exp.}$ = 3.54 g/cm³, d_x = 3.68 g/cm³; space group D_{2h}^{16}–Pnma

4 Ba in 4c with x = 0.014, y = 0.250, z = 0.694

4 Ba in 4c with x = 0.839, y = 0.250, z = 0.095

4 Si in 4c with x = 0.424, y = 0.250, z = 0.091

4 Si in 4c with x = 0.205, y = 0.250, z = 0.969

8 Si in 8d with x = 0.190, y = 0.078, z = 0.147

Received, April 8th, 1963 [Z 483/313 IE]
German version: Angew. Chem. 75, 451 (1963).

[1] *L. Wöhler* and *W. Schuff*, Z. anorg. allg. Chem. *209*, 33 (1932).

[2] *G. Rocktäschel* and *A. Weiss*, Z. anorg. allg. Chem. *316*, 231 (1962).

[3] *G. Rocktäschel*, Ph. D. Thesis, Technische Hochschule Darmstadt, 1962.

[4] *E. Hellner*, Z. anorg. allg. Chem. *261*, 226 (1950).

[5] *J. Böhm* and *O. Hassel*, Z. anorg. allg. Chem. *160*, 152 (1927).

A New Synthesis of Bis-perchloroallene

By Dr. G. Maaß

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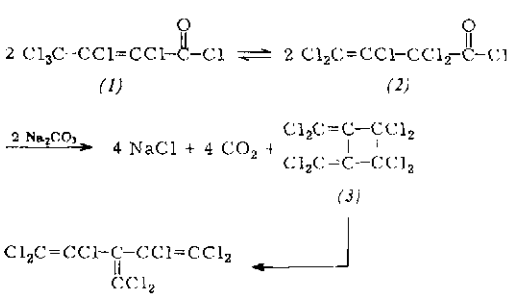
Marl/Kreis Recklinghausen (Germany)

Bis-perchloroallene (1,2-bis-dichloromethylene tetrachlorocyclobutane) *(3)* can be prepared by dehydrochlorination of pentachloropropene with KOH in boiling toluene [1] or with $NaNH_2$ in liquid NH_3 [2]. It is also obtained in small yields by alkali degradation of ethyl perchlorocrotonate or ethyl perchlorovinylacetate [3]. Perchlorocrotonyl chloride *(1)* or perchlorovinylacetyl choride *(2)* yields exclusively bis-perchloroallene in the presence of strong tertiary bases (*e.g.* trimethylamine) or solid Na_2CO_3.



Organic compounds in the presence of which the reaction takes place, are (in order of diminishing activity) *e.g.* dimethylformamide, dimethylacetamide, formamide, acetamide, acetone, furfural, ethyl acetoacetate, ethyl acetate, tetrahydrofuran, dioxan. The reaction with Na_2CO_3 in the presence of the first members of the series is strongly exothermic. It can be moderated by inert solvents (ether, hydrocarbons). Heat strongly accelerates the reaction in the presence of the last members of the foregoing series. With the water-soluble N-free adjuvants (acetone, dioxan), the rate of reaction is also considerably raised by addition of water. The bis-perchloroallene *(3)* – also referred to as δ-C_6Cl_8 – (m.p. 93 °C from ethanol) obtained in almost quantitative yield rearranges quantitatively to the ε-C_6Cl_8 *(4)*, m.p. 44 °C, on heating for 30 min. at 230 °C.

Received, April 8th, 1963 [Z 485/322 IE]
German version: Angew. Chem. 75, 451 (1963).

[1] *H. J. Prins*, J. prakt. Chem. (2) *89*, 421 (1914).

[2] *A. Roedig* and *F. Bischoff*, Naturwissenschaften *49*, 448 (1962).

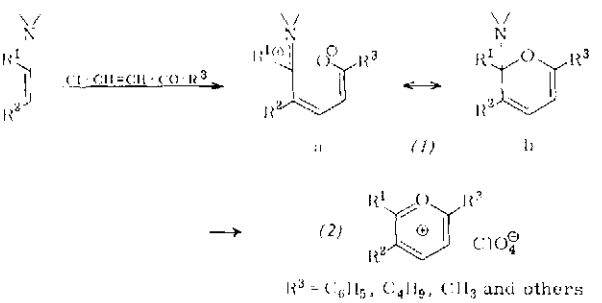
[3] *A. Roedig* and *P. Bernemann*, Liebigs Ann. Chem. *600*, 10 (1956).

Reaction of Enamines with β-Chlorovinyl Ketones [1]

By Dr. W. Schroth and Dipl.-Chem. Gerhard Fischer

Institut für Organische Chemie der Universität Leipzig (Germany)

Enamines react with β-chlorovinylketones to give colored, occasionally crystalline compounds of type *(1)*. The absence of the C=O band in the usual carbonyl region indicates mesomerism between the limiting structures a and b.

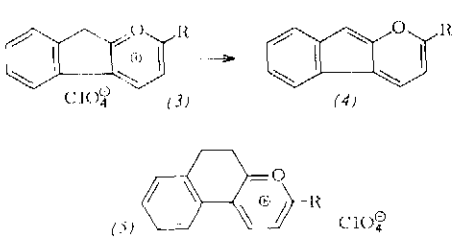


$R^3 = C_6H_5$, C_4H_9, CH_3 and others

These compounds can be protonated and acylated reversibly. The pyrylium perchlorate *(2)* is found with perchloric acid. The yields of *(1)* lie between 75 and 95 %, and those of *(2)* between 50 and 60 %.

Enamines derived from aldehydes give 2,5-disubstituted pyrylium salts, *e.g.* *N*-diethylamino-1-butene reacts with phenyl β-chlorovinyl ketone to give 5-ethyl-2-phenylpyrylium perchlorate, m.p. 152–153 °C.

Enamines derived from cyclic ketones lead to bicyclic pyrylium salts, *e.g.* 1-piperidinocyclopentene leads via *(1)* [R^1–R^2 = $-(CH_2)_3-$, $R^3 = C_6H_5$, red needles, m.p. 112–113 °C] to the corresponding pyrylium salt *(2)*, m.p. 161–162 °C; 1-piperidinocyclohexene leads to *(2)* [R^1–R^2 = $-(CH_2)_4-$, $R^3 = C_6H_5$, m.p. 177–178 °C]; and 1-piperidinocycloheptene leads to *(2)* [R^1–R^2 = $-(CH_2)_5-$, $R^3 = C_6H_5$, m.p. 146 to 147 °C].



Whereas the compound *(1)* [$R^3 = C_6H_5$, red needles, m.p. 148 °C] obtained from 1-pyrrolidinoindene resists conversion into the corresponding pyrylium perchlorate, that [*(1)*, $R^3 = C_6H_5$, orange-red needles, m.p. 133–134 °C] from 2-piperidinoindene is readily converted into the indeno[1,2-*b*]pyrylium salt *(3)* [R = C_6H_5, m.p. 215 °C] and to the indeno[1,2-*b*]-pyran *(4)* [R = C_6H_5, dark brown platelets, m.p. 197–198 °C].

The enamine obtained from β-tetralone and piperidine forms the pyrylium perchlorate *(5)* [R = C_6H_5, m.p. 210 °C (decomp.)] via *(1)* [R^3 = C_6H_5, yellow needles, m.p. 115–116 °C]. The pyridine derivative obtained from the pyrylium salt melts at 130 °C.

Received, April 22nd, 1963 [Z 493/326 IE]
German version: Angew. Chem. 75, 574 (1963).

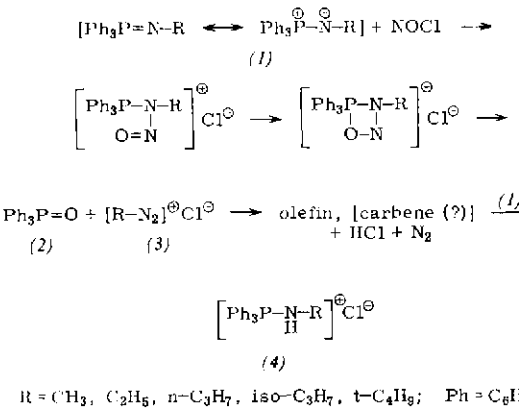
[1] Communication No. 3 on Pyrylium Compounds; Communication No. 2: *G. Fischer* and *W. Schroth*, Z. Chem., in the press.

The Reaction of Triphenylphosphine Imines with Nitrosyl Chloride

By Prof. Dr. H. Zimmer and G. Singh, M. S. [*]

Department of Chemistry, University of Cincinnati, Cincinnati 21, Ohio (U.S.A.)

A recent publication [1] dealing with reactions of triphenylphosphine with NOCl prompts us to report about the interaction of triphenylphosphineimines *(1)* with this reagent. Derivatives of *(1)* substituted with aliphatic groups react in ethylene glycol dimethyl ether with absolute exclusion of moisture in a strongly exothermic reaction at −70 °C according to Scheme 1.



Scheme 1

In all the cases examined, compounds of type *(4)* (see Table 1) were isolated together with *(2)*.

The volume of nitrogen evolved was measured for R = t-C_4H_9 (1.66 of Ph_3P=NR and 0.164 g of NOCl gave 61 ml of N_2; calc. 62.8 ml). The structure of the alkylaminotriphenylphosphonium chlorides was proved as follows: a) by elemental analysis b) by hydrolysis to alkylamines and *(2)*; and c) by synthesis from *(1)* and gaseous HCl in ether [2].

In order to determine whether diazonium chlorides are actually formed as intermediates, triphenylphosphine phenylimine was treated with NOCl. As anticipated, the diazonium salt corresponding to *(3)* could be isolated without difficulty. It was coupled with β-naphthol; the dyestuff produced was identical with authentic 1-phenylazo-2-naphthol, m.p. 131 °C ([3] gives m.p. 132–133 °C).

Received, April 25th, 1963 [Z 496/321 IE]
German version: Angew. Chem. 75, 574 (1963).

Table 1. Alkylaminotriphenylphosphonium chlorides.

R	m.p. [a] [°C]	Yield [b] [%] (4)	Yield [b] [%] (2)	Empirical formula (4)	Analyses [c] Calc. C	Calc. H	Calc. N	Found C	Found H	Found N
CH_3	216–217	92	95	$C_{19}H_{19}ClNP$	69.62	5.80	—	69.26	5.92	—
C_2H_5	268–270	95	94	$C_{20}H_{21}ClNP$	70.28	6.14	4.09	70.71	6.01	3.90
n-C_3H_7	190–191	96	88	$C_{21}H_{23}ClNP{\cdot}H_2O$ [d]	67.47	6.69	3.74	67.33	6.72	3.78
iso-C_3H_7	230–231	91	86	$C_{21}H_{23}ClNP$ [e]	70.89	6.47	—	71.10	6.55	—
t-C_4H_9	202–203	93	93	$C_{22}H_{25}ClNP{\cdot}H_2O$ [f]	68.12	6.96	3.61	68.44	6.82	3.81

[a] All melting points are uncorrected.
[b] The yields are calculated according to Scheme 1.
[c] The analyses were carried out by *A. Bernhardt*, Max-Planck-Institut Mülheim/Ruhr (Germany) and by Galbraith Laboratories, Knoxville 21, Tennessee (U.S.A.).
[d] Calcd. Cl 9.50; P 8.29; found Cl 9.25; P 8.15.
[e] Identified by agreement with properties of material prepared by direct synthesis from *(1)* with R = iso-C_3H_7.
[f] Calcd. Cl 9.16; P 8.00; found Cl 9.30; P 8.11.

[*] The authors wish to express their thanks to the U.S.Army, Office of Ordnance Research, for financial support.

[1] *D. Klamann* and *P. Weyerstahl*, Angew. Chem. 75, 89 (1963); Angew. Chem. internat. Edit. 2, 43 (1963).

[2] *H. Zimmer* and *G. Singh*, J. org. Chemistry 28, 483 (1963).

[3] *M. Betti*, Gazz. chim. ital. 30, 164 (1900).

Preparation and Properties of Tin(II) Methoxide and Tin(II) Tetrahydroborate

By Priv.-Doz. Dr. E. Amberger and Dr. Maria-Regina Kula

Institut für Anorganische Chemie der Universität München (Germany)

Tin(II) methoxide, the first alkoxy compound of bivalent tin, was obtained in 85 % yield by treating tin(II) bromide with sodium methoxide in absolute methanol while excluding air and moisture.

$$SnBr_2 + 2\ NaOCH_3 \rightarrow Sn(OCH_3)_2 + 2\ NaBr$$

The methoxide was precipitated as white amorphous flakes which are insoluble in methanol and which were therefore washed repeatedly with absolute methanol until free from halide. Tin(II) methoxide decomposes with discoloration and without melting at above 100 °C. It is easily hydrolysed and oxidized.

Tin(II) tetrahydroborate is formed on passing excess diborane through a suspension of tin(II) methoxide in diethyl ether at −78 °C.

$$2\ Sn(OCH_3)_2 + 3\ B_2H_6 \rightarrow 2\ Sn(BH_4)_2 + 2\ HB(OCH_3)_2$$

After distilling off the diethyl ether, diborane, and dimethoxyborine, the tin(II) tetrahydroborate, which is moderately soluble, was extracted from the solid residue using dimethyl ether. Tin(II) tetrahydroborate is a dark yellow solid and decomposes at above −65 °C to yield tin, diborane, and hydrogen. On warming rapidly to room temperature, the compound decomposes, usually explosively, to form the elements. It is not volatile *in vacuo* at −65 °C.

Received, April 19th, 1963 [Z 487/314 IE]
German version: Angew. Chem. 75, 476 (1963).

The Constitution of "Tetraphenylpentatetraene"[1]

By Prof. Dr. Richard Kuhn and Bernhard Schulz

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The structure *(1)* has been ascribed [2,3] to a yellow hydrocarbon which can be obtained in different ways. We have found that this hydrocarbon is also formed by the action of

N-bromosuccinimide or dibromodimethylhydantoin on *(2)* [4] and subsequent treatment with pyridine (yield *ca.* 15 %). Accordingly, the so-called "pentatetraene" has the constitution *(3)* of tetra-(β,β-diphenylvinyl)ethylene, in agreement with its NMR spectrum, molecular-weight measurements, and other results.

(1) $(C_6H_5)_2C{=}C{=}C{=}C{=}C(C_6H_5)_2$

(2) $(C_6H_5)_2C{=}CH{-}CH{-}CH{=}C(C_6H_5)_2$

$(C_6H_5)_2C{=}CH{-}\underset{|}{C}H{-}CH{=}C(C_6H_5)_2$

(3) $(C_6H_5)_2C{=}CH{-}C\ \ CH{-}C(C_6H_5)_2$

$(C_6H_5)_2C{=}CH{-}\underset{|}{C}\ \ CH{-}C(C_6H_5)_2$

So far, all attempts to prepare genuine pentatetraenes have resulted in ring-closure to yield derivatives of indene [1] or dimerisation with or without partial hydrogenation.

Received, April 29th, 1963 [Z 492/325 IE]
German version: Angew. Chem. *75*, 452 (1963).

[1] Communication No. XV on Cumulenes; Communication No. XIV: *R. Kuhn* and *B. Schulz*, Angew. Chem. *74*, 292 (1962); Angew. Chem. internat. Edit. *1*, 211 (1962).

[2] *F. Bohlmann* and *K. Kieslich*, Abh. braunschweig. wiss. Ges. *1957*, IX, 147.

[3] *G. Marin*, Thèse Ingenieur Docteur, Paris 1960. See also: *P. Cadiot*, *W. Chodkiewicz*, and *J. Rauss-Godineau*, Bull. Soc. chim. France *1961*, 2176.

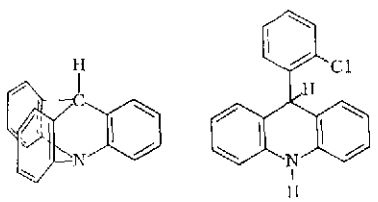
[4] *G. Wittig* and *B. Obermann*, Ber. dtsch. chem. Ges. *68*, 2214 (1935). The structure given there is in agreement with the NMR spectrum of *(2)* and its conversion by us into the octahydro compound (m.p. 181 °C).

Azatriptycene

By Prof. Dr. G. Wittig and Dr. G. Steinhoff

Institut für Organische Chemie der Universität Heidelberg (Germany)

Following the synthesis of benzoazatriptycene [1], we have now succeeded in preparing azatriptycene *(1)* in another way. By application of the synthesis principle of ring-closing a dehydrobenzene intermediate [2], the compound *(1)*, m.p. 266–267 °C, is obtained in 54 % yield by treating 9-*o*-chlorophenyl-9,10-dihydroacridine *(2)* with KNH_2 in liquid NH_3.



(1) *(2)*

In the case of the analogous preparation of the compound *(1)* from 9-*m*-chlorophenyl-9,10-dihydroacridine *(3)*, the yield dropped to 17 %. Compounds *(2)* and *(3)* were made according to *Bernthsen* [3] by treating diphenylamine with the corresponding chlorobenzoic acid and subsequent reduction. Infrared, ultraviolet, and nuclear magnetic resonance spectra established the structure of *(1)*. The ultraviolet spectrum of *(1)* was, as expected, in complete accord with that of the isosteric compound triptycene [*(1)*, CH instead of N]; on mixing *(1)* with triptycene (m.p. 256 °), no depression of the m.p. was observed. The formation of the methiodide of *(1)* in methyl iodide at room temperature – isolated as its tetraphenyl borate, m.p. 289.5–291 °C (decomp.) – demonstrates that the amine *(1)* is much more basic than triphenylamine.

Received, May 2nd, 1963 [Z 494/327 IE]
German version: Angew. Chem. *75*, 453 (1963).

[1] *G. Wittig* and *G. Steinhoff*, Chem. Ber. *95*, 203 (1962).

[2] Cf. *G. Wittig* and *L. Pohmer*, Chem. Ber. *89*, 1337 (1956); *R. Huisgen* and *J. Sauer*, Angew. Chem. *72*, 97 (1960); *J. F. Bunnett*, J. chem. Educ. *38*, 282 (1961).

[3] *A. Bernthsen*, Liebigs Ann. Chem. *224*, 1 (1884).

Cobalt(II) Cyanide, its Three-dimensional Framework Structure and Zeolitic Compounds

By Prof. Dr. Armin Weiss and cand. chem. W. Rothenstein

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The flesh-colored, hydrated form and the deep blue, anhydrous form of $Co(CN)_2$ both yield identical X-ray diagrams indicating a cubic structure with a cell parameter of 10.12 Å. Since the hydrated form contains up to about 3 moles of H_2O in the interior of the crystal, there must be large cavities present in anhydrous $Co(CN)_2$.

This is supported by its ability to form inclusion or zeolitic compounds with a wide range of polar compounds X such as n-alcohols, nitriles, aldehydes, carboxylic acids, amines, aryl halides, *etc.* These zeolitic compounds are characterized not by a fixed molar ratio of $Co(CN)_2$:X, but by a constant volume ratio $V_{Co(CN)_2}$:V_X. About 30 ml of each can be absorbed per mole of anhydrous $Co(CN)_2$. The formation of zeolitic compounds can readily be explained by reference to the crystal structure of $Co(CN)_2$. It exists as a three-dimensional, coarse-meshed framework of $Co(CN)^-_3$ (Fig. 1).

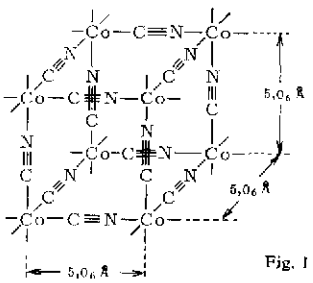

Fig. 1

To fulfil the conditions of stoichiometry for $Co(CN)_2$, every second cube contains a Co^{2+} ion. The structure of $Co(CN)_2$ can therefore be represented as $Co[Co(CN)_3]^-_2$. It cannot be decided by X-ray analysis whether the Co atoms in the three-dimensional skeleton are surrounded alternately by 6C or 6N atoms (*i.e.* whether $[Co(CN)_6]^{4-}$ occurs) or by 3C and 3N atoms together. Molecules whose least van der Waals diameter substantially exceeds 3.6 Å cannot penetrate into the framework. Hence $Co(CN)_2$ has the properties of a molecular sieve.

The structure is similar to those of $Fe^{2+}_3[Fe^{3+}(CN)_6]_2$ and $Co^{2+}_3[Co^{3+}(CN)_6]_2$ [1, 2]. $Co(CN)_2$ can also absorb HCN molecules into the interior of the crystal and thus, on the basis of an analytical Co:CN ratio $>1:2$, can simulate partial oxidation of Co^{2+} to Co^{3+}.

Received, May 6th, 1963 [Z 499/328 IE]
German version: Angew. Chem. *75*, 575 (1963).

[1] *J. F. Keggin* and *F. D. Miles*, Nature (London), *137*, 577 (1936).

[2] *A. Vaciago* and *A. Mugnoli*, Accad. naz. Sincei, Rend., Cl. Sci. fisiche, mat. Natur 8, *25*, 531 (1958).

A New Synthesis of Fulvenes [1]

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Previously, it was only possible to prepare fulvenes in yields of 80 % at the best by condensing cyclopentadiene or analogous compounds with carbonyl compounds in the presence of strong alkalis. The products contained considerable amounts of resinous impurities. We now use primary or secondary amines as condensing agents. The catalytic activity of the amines probably results from their ability to react with carbonyl compounds to form imines or, in the presence of monomeric cyclopentadiene, Mannich bases.

Condensation of primary aliphatic amines with aliphatic aldehydes or ketones at room temperature rapidly gives Schiff bases, equilibrium being set up in the reaction mixture. Furthermore, it is known that compounds containing acidic protons add onto the C=N double bond to give Mannich bases which, under certain conditions, decompose with elimination of amine. The fulvene synthesis described here appears to be a combination of these known reactions.

Any amine which can participate in a Mannich reaction will, in principle, act as a catalyst. The catalytic activity is not, however, limited to these nitrogen compounds. The reaction also occurs smoothly in the presence of, for example, methylhydrazine or phenylhydrazine. Phenylhydrazones also react with cyclopentadiene at room temperature to give fulvenes. Aldehydes and ketones are equally suitable as carbonyl components.

Unsaturated aldehydes such as crotonaldehyde also react with cyclopentadiene in the presence of a small amount of amine to give the corresponding unsaturated fulvenes.

All compounds containing a methylene group between two double bonds are suitable as diene components. The condensation proceeds at a satisfactory rate in aqueous media at room temperature to give fulvenes in quantitative yield. For example, 1 mole of monomeric cyclopentadiene is mixed with 1 mole of acetone, and 0.15 mole of methylamine is added as an approx. 30 % aqueous solution. Within about 30 min. the reaction mixture separates into two phases, the upper layer being almost pure 6,6-dimethylfulvene containing a small amount of dissolved amine.

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German version: Angew. Chem. 75, 576 (1963).

[1] Corresponding patents filed.

Synthesis of α-Oxothiocarboxamides

By Prof. Dr.-Ing. F. Asinger and F. Gentz

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To our knowledge, *N*-unsubstituted α-oxothiocarboxamides *(1)* (R = Ar or Alk) have not been previously prepared. According to *Thesing* [1], addition of hydrogen sulfide onto acylcyanides, R–CO–CN, succeeds when the substituent R is an electron-donor (*e.g.* R = R'NH or CH_3O). We have found that base-catalysed addition of H_2S onto acyl- or aroylcyanides proceeds in good yields according to the equation

$$R\cdot CO\cdot CN \xrightarrow[(C_2H_5)_3N]{H_2S} R\cdot CO\cdot CSNH_2 \qquad (1)$$

under suitable conditions, which occasionally must be varied to fit individual cases.

The α-oxothiocarboxamides listed below were prepared as follows: An approximately 20 % solution of the acylcyanide in dry ether containing a few drops of triethylamine is saturated at 0 °C with H_2S, allowed to attain room temperature. After 30 min. the excess hydrogen sulfide and the ether are removed *in vacuo*, and the residue recrystallized. 4,4-Dimethyl-2-oxothiovaleramide [*(1)* R = $(CH_3)_3CCH_2$], deep orange-red crystals, m.p. 76 °C (from n-heptane), yield 94 %; 2,4-dinitrophenylhydrazone, m.p. 152 °C (from ethanol) [2]. 4-Methyl-2-oxothiovaleramide [*(1)* R = $(CH_3)_2CH-CH_2$], orange-red crystals, m.p. 35 °C (from light petroleum), yield 84 %. Phenylglyoxylthioamide [*(1)* R = C_6H_5], yellow crystals, m.p. 97.5–98 ° (from water), yield 66 %.

Received, May 8th, 1963 [Z 502/329 IE]
German version: Angew. Chem. 75, 577 (1963).

[1] *J. Thesing*, Angew. Chem. *68*, 338 (1956).

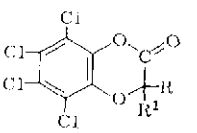
[2] The starting material, 4,4-dimethyl-2-oxovaleronitrile [b.p. 41–45 °C/12 mm; n_D^{20} = 1.4100; 2,4-dinitrophenylhydrazone, m.p. 127–128 °C (from ethanol)], has not been previously described. It was synthetized in 51% yield by treating 3,3-dimethylbutyroyl bromide with $Cu_2(CN)_2$.

Ketene Capture by *o*-Quinones

By Prof. Dr. W. Ried and Dipl.-Chem. W. Radt

Institut für Organische Chemie der Universität Frankfurt/Main (Germany)

Ketenes add onto *o*-quinones in the cold to give cyclic lactones *(1)* [1]. This reaction is suitable for trapping ketenes which occur as unstable intermediates during thermolysis of *o*-quinone diazides (6-diazo-2,4-cyclohexadien-1-ones) and diazoketones. Aldoketenes, which are usually inaccessible, also add onto *o*-quinones. The *o*-diazocarbonyl compounds given in Table 1 were treated with tetrachloro-*o*-quinone to give the corresponding lactones.

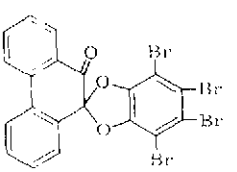


(1)

Table 1.

o-Quinone diazide	M. p. of lactone [°C]
Phenanthroquinone diazide	307
Chrysoquinone diazide	306–308
2-Nitrophenanthroquinone diazide	310–312
Benzoyldiazomethane	185–187

If tetrabromo-*o*-quinone, which is more reactive, is substituted for tetrachloro-*o*-quinone, the ketene precursors produced by elimination of nitrogen from the *o*-quinone diazides enumerated in Table 2, are captured as their quinone acetals *(2)* before they can undergo the "Wolf rearrangement" to ketenes. In contrast to the lactones, which are colorless, the quinone acetals are bright yellow. Their structures were confirmed by hydrolysis with acid to reform the original quinones.



(2)

Table 2.

o-Quinone diazide	M. p. of quinone acetal [°C]
Phenanthroquinone diazide	280–282
Chrysoquinone diazide	304–305

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German version: Angew. Chem. 75, 638 (1963).

[1] *L. Horner, E. Spietschka*, and *A. Gross*, Liebigs Ann. Chem. *573*, 17 (1951).

A Convenient Synthesis of Alkoxycyclopropanes

By Doz. Dr. U. Schöllkopf and Dipl.-Chem. J. Paust

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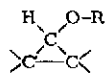
We have obtained alkoxycyclopropanes *(1)* in good yield by treating dichloromethyl alkyl ethers [1] in olefins with methyl-lithium in ether until a positive Gilman test was obtained. The methyl-lithium must be made from methyl iodide, *i.e.* it must contain lithium iodide.

It is very likely that first one chlorine atom of the dichloromethyl alkyl ether is exchanged for iodine in a nucleophilic reaction, then a halogen-metal exchange with the methyl-lithium takes place with formation of a lithiochloromethyl alkyl ether, the latter then decomposing to form alkoxy-

carbene and lithium chloride. Finally, the carbene adds onto the olefinic double bond [2].



(1) R = alkyl

The formation of the cyclopropane derivative takes place in a stereospecific manner as a *cis*-addition.

1-Vinyl-2-n-hexoxycyclopropane: A solution in ether of 0.14 mole of methyl-lithium (prepared from methyl iodide a 1.2 N solution) is added dropwise over 2 hours at −5 °C to a stirred solution of 18.5 g (0.1 mole) of dichloromethyl n-hexyl ether in 100 ml of butadiene. After hydrolysis with 100 ml of water, the ether layer is separated off, thoroughly washed with water, and dried over calcium chloride. Distillation yields 12.7 g of 1-vinyl-2-n-hexoxycyclopropane, b.p. 122 °C/65 mm (isomer ratio 1.3:1).

Table 1. Alkoxycyclopropanes (R = CH_3, R' = n-C_6H_{13})

Olefin	Reaction temp. [°C]	Product	Yield [%] R	Yield [%] R'
Isobutene	−10	1,1-dimethyl-2-alkoxycyclopropane	55	79
Cyclohexene	+25 −10	*exo/endo*-7-alkoxynorcarane [a]	32 32	36
trans-2-Butene	−10	*trans*-1,2-dimethyl-3-alkoxycyclopropane	52	
cis-2-Butene	−10	*exo/endo-cis*-1,2-dimethyl-3-alkoxycyclopropane [b]	49	
Butadiene	−5	*exo/endo*-1-vinyl-2-alkoxycyclopropane	65	76
Cyclopentadiene	−5	*exo/endo*-6-alkoxybicyclo-[3,1,0]hex-2-ene	50	65

[a] *exo*-adduct in higher yield (NMR spectrum).
[b] *endo*-adduct in higher yield (NMR spectrum).

Received, May 27th, 1963 [Z 517/341 IE]
German version: Angew. Chem. *75*, 670 (1963).

[1] *H. Gross* et al., Chem. Ber. *94*, 544 (1961).
[2] Cf. *U. Schöllkopf* et al., Tetrahedron Letters *1962*, 241.

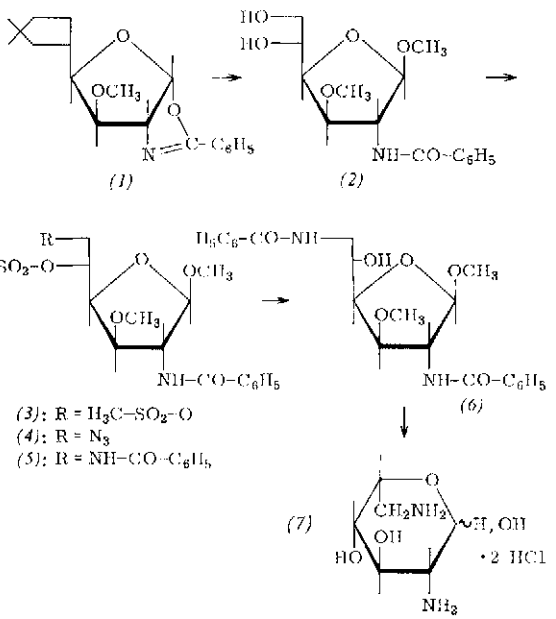
Synthesis of 2,6-Diamino-2,6-dideoxy-L-idose [1]

By Dr. W. Meyer zu Reckendorf

Department of Chemistry, Stanford University, Stanford, California (USA)

Two 2,6-diamino-2,6-dideoxyhexoses were isolated from Neomycin B [2] and Paromomycin [3] which proved to be identical [4] and for which the constitution of 2,6-diamino-2,6-dideoxy-L-idose was proposed [5].The proof of this structure [6] by degradation to 5-acetamino-5-deoxy-L-xylofuranose prompts us to report its synthesis.

Treatment of the blocked oxazoline *(1)* [7] with 5×10^{-4} N methanolic hydrochloric acid [8] gave methyl 2-benzamino-2-deoxy-3-*O*-methyl-β-D-glucofuranoside*(2)* in excellent yield. This was dimesylated and converted with sodium azide in dimethyl sulfoxide [9] into the azide *(4)*, from which the benzamide *(5)* was formed by reduction and benzoylation. Analogous pyranoses have already been synthetized by us [9]. Treatment of *(5)* with sodium acetate in 95 % ethanol [10] gave a syrup *(6)*, which on treatment with boron trichloride in dichloromethane [11] and hydrolysis with 6 N hydrochloric acid afforded a quantitative yield [calculated on *(5)*] of the free diamino sugar *(7)* in the form of its hydrochloride. Chromatographic purification produced a colorless hygroscopic powder, $[\alpha]_D^{24} = +17.8°$ (c = 1.18 in water); [2,3] give $[\alpha]_D^{24} = +17.5°$, +19° in water. *N*-Acetylation and reduction with $NaBH_4$ afforded the *N,N'*-diacetyl-dihydro derivative,



(3): R = H_3C-SO_2-O
(4): R = N_3
(5): R = $NH-CO-C_6H_5$

which crystallized in large prisms, m.p. 148–149 °C; [3] gives 150.5–151.5 °C; $[\alpha]_D^{24} = -19.2°$ (c = 0.5 in water); [3] gives −17.8° (c = 4.0 in acetate buffer).

The agreement of the physical data justifies the assumption that the synthetic product is identical with Neosamine B and Paromose. The constitution of all constituents of the Neomycin complex is thereby clarified.

Received, April 22nd, 1963 [Z 491/324 IE]
German version: Angew. Chem. *75*, 573 (1963).

[1] Communication No. III on Diamino-sugars; Communication No. II, see [9]; thanks are accorded to the National Institutes of Health, U.S. Public Health Service, for Grant No. GM 10541-01 in support of this work.

[2] *K. L. Rinehart, A. D. Argoudelis, W. A. Goss, A. Sohler*, and *C. P. Schaffner*, J. Amer. chem. Soc. *82*, 3938 (1960).
[3] *T. H. Haskell, J. C. French*, and *Q. R. Bartz*, J. Amer. chem. Soc. *81*, 3480 (1959).
[4] *S. Hanessian*, personal communication.
[5] *K. L. Rinehart, M. Hichens, A. D. Argoudelis, W. S. Chilton, H. E. Carter, M. P. Georgiadis, C. P. Schaffner*, and *R. T. Schillings*, J. Amer. chem. Soc. *84*, 3218 (1962).
[6] *T. H. Haskell* and *S. Hanessian*, 144th Meeting Amer. chem. Soc., 1963, 19C.
[7] *R. Gigg* and *P. M. Carroll*, Nature (London) *191*, 495 (1961).
[8] *S. Konstas, I. Photaki*, and *L. Zervas*, Chem. Ber. *92*, 1288 (1959).
[9] *W. Meyer zu Reckendorf*, Chem. Ber., in the press.
[10] *B. R. Baker* and *R. E. Schaub*, J. org. Chemistry *19*, 646 (1954).
[11] *T. G. Bonner, E. J. Bourne*, and *S. McNally*, J. chem. Soc. (London) *1960*, 2929.

Isolation of Trimethyltitanium Iodide

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On treatment of $Ti(CH_3)_4$ with CF_3I at low temperatures, $(H_3C)_3TiI$ is formed. Compounds of composition $(CF_3)_n Ti(CH_3)_{4-n}$ (n = 1–4) are not obtained.

Gaseous CF_3I purified by several recondensations was passed into bright yellow solutions of pure $Ti(CH_3)_4$ in ether/n-hexane (2:1) at −78 °C. On warming to about −50 °C, the solutions became brownish in color. After partial evaporation *in vacuo* at approximately −65 °C, yellow needles of $(H_3C)_3TiI$ separated out on the walls of the flask; these are stable only at low temperatures and in the absence of air and moisture.

For analytical purposes, evaporation was continued to dryness and the total residue decomposed with water. Only one gaseous decomposition product was formed, namely methane, its presence being established by infrared spectroscopy. The volume of CH_4 was determined by measurement of pressure. The aqueous solution of the residue was transparent; its acid reaction (pH approx. 2) is due to the presence of hydroiodic acid. The average value for the ratio of $HI:CH_4$ was 1:2.95. The titanium content, which was determined gravimetrically, was somewhat too high owing to thermal decomposition.

No unequivocal statement can yet be made about the course of the reaction. However, the occurrence of CH_3I as a reaction product indicates that a CH_3 group of the $Ti(CH_3)_4$ is not simply exchanged for the iodine atom of CF_3I.

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German version: Angew. Chem. 75, 576 (1963).

A New Process for the Formation of P-P Bonds

By Doz. Dr. W. Kuchen and Dipl.-Chem. W. Grünewald

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PBr_3 and $PSBr_3$ react with magnesium in diethyl ether to give $MgBr_2$-etherate and red phosphorus [1] as well as a product with the overall composition $(PS)_x$ [2]. Analogously, tetraphenylcyclotetraphosphine [3] and tetraphenyldiphosphine [4] are formed from $C_6H_5PBr_2$ and $(C_6H_5)_2PBr$, respectively, in good yield.

$$C_6H_5PBr_2 + Mg \rightarrow {}^1/_4\,(C_6H_5P)_4 + MgBr_2 \quad (1)$$

$$2\,(C_6H_5)_2PBr + Mg \rightarrow (C_6H_5)_2P{-}P(C_6H_5)_2 + MgBr_2 \quad (2)$$

These reactions occur smoothly even at room temperature. An ether/benzene mixture is used as solvent, and the $MgBr_2$ dissolved in the reaction solution as the etherate is precipitated by addition of dioxan.

Treatment of the reaction mixture obtained according to equation 2 with sulfur leads to practically quantitative yields of tetraphenyldiphosphine di-*P*-sulfide $(C_6H_5)_2P(S){-}P(S)(C_6H_5)_2$ [4]. The phenylphosphorus bromides required for the reaction are easily prepared by equilibrating the chlorides, which are readily available, with PBr_3 at 100–200 °C and then continuously distilling both PCl_3 and the phosphorus chlorobromides $PBr_{3-n}Cl_n$ ($n = 1$ or 2) which are also formed out of the equilibrium mixture. The yields of $C_6H_5PBr_2$, b.p. 124 to 126 °C/11 mm, and $(C_6H_5)_2PBr$, b.p. 140–141 °C/35 mm are approximately 90 %.

The reaction of phosphorus bromides with magnesium thus provides a further means of synthetizing P-P bonds and supplements the few preparative methods so far available [5].

Received, May 9th, 1963 [Z 501/333 IE]
German version: Angew. Chem. 75, 576 (1963).

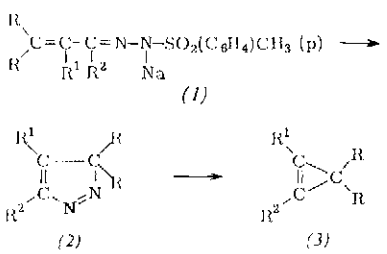
[1] *W. Kuchen* and *H. G. Beckers*, unpublished experiments.
[2] *W. Kuchen* and *H. G. Beckers*, Angew. Chem. *71*, 163 (1959).
[3] *W. Kuchen* and *H. Buchwald*, Chem. Ber. *91*, 2296 (1958).
[4] *W. Kuchen* and *H. Buchwald*, Chem. Ber. *91*, 2871 (1958).
[5] Review: *J. E. Huheey*, J. chem. Educat. *40*, 153 (1963).

Preparation of Pyrazolenines and their Photolysis to Cyclopropenes

By Prof. Dr. G. L. Closs and Dr. W. Böll

George Herbert Jones Laboratory, The University of Chicago, Chicago (U.S.A.)

We observed ring closure of *N*-sodium salts of *p*-toluenesulfonylhydrazones of α,β-unsaturated carbonyl compounds *(1)* [1] followed by elimination of sodium toluenesulfinate to give pyrazolenines *(2)*. On heating *(1a) in vacuo* in triethyleneglycol dimethyl ether, *(2a)* distilled in 36 % yield from the reaction mixture. The structure assignment of *(2a)* (b.p. 75 °C/51 mm) is based on spectral data (infrared; strong band at 1640 cm^{-1}, –C–H 3095 cm^{-1}, ultraviolet: $\lambda_{max} = 257$ mμ, $\varepsilon = 2250$; 350 mμ, $\varepsilon = 270$; NMR: singlet 8.65 τ, doublet 7.63 τ, quadruplet 3.70 τ, $J = 1.6$ cps) [2]. On heating solid *(1b) in vacuo* to 130 °C, *(2b)* was obtained in 68 % yield (b.p. 63 °C/0.025 mm; infrared: strong band at 1652 cm^{-1}; ultraviolet: $\lambda_{max} = 272$ mμ, $\varepsilon = 3530$; 347 mμ, $\varepsilon = 300$; NMR: singlet 8.78 τ, multiplets at 8.28, 7.72, and 7.03 τ) [2].



(1)

(2) *(3)*

(a) $R = R^2 = CH_3$; $R^1 = H$
(b) $R = CH_3$; $R^1 = R^2 = -(CH_2)_5-$

Both *(2a)* and *(2b)* are stable under conditions leading to pyrolytic rearrangements of phenylsubstituted pyrazolenines [3]. Compound *(2a)* distills unchanged at 147–148 °C/760 mm and *(2b)* can be distilled *in vacuo* at 225 °C.

Irradiation with a Hanovia high pressure mercury lamp at 13 °C led to formation of cyclopropenes *(3)* by elimination of nitrogen. The known 1,3,3-trimethylcyclopropene *(3a)* [4] was obtained from *(2a)* in 65 % yield. Compound *(2b)* gave an almost quantitative yield of the new bicyclic compound *(3b)* (b.p. 56 °C/12 mm). The structure of *(3b)* follows unambiguously from its infrared spectrum (band at 1840 cm^{-1} (m), a region typical for cyclopropene skeletal vibrations [4]) and its NMR spectrum (singlet at 8.85 τ and multiplets at 8.25 and 7.70 τ) [2].

Received, May 15th, 1963 [Z 505/335 IE]
German version: Angew. Chem. 75, 640 (1963).

[1] *G. L. Closs* and *L. E. Closs*, J. Amer. chem. Soc. *83*, 2015 (1961).

[2] Satisfactory elemental analyses were obtained for these compounds.

[3] *J. van Alphen*, Recueil Trav. chim. Pays-Bas *62*, 485 (1943); *R. Hüttel, J. Riedl, H. Martin*, and *K. Franke*, Chem. Ber. *93*, 1425, 1433 (1960).
[4] *G. L. Closs* and *L. E. Closs*, J. Amer. chem. Soc. *83*, 1003 (1961).

Distillable N-Hemiacetals: N-α-Hydroxyalkyl-N,O-dialkylhydroxylamines [1]

By Prof. Dr. G. Zinner and Apotheker W. Ritter

Institut für Pharmazeutische Chemie und Lebensmittelchemie der Universität Marburg/Lahn (Germany) [2]

On treatment of *N,O*-dimethylhydroxylamine *(1)* with aldehydes in a molar ratio of 2:1, we obtained – in addition to the anticipated acetals *(2)* – the corresponding hemiacetals *(3)* in yields 30–50 %.

$$RO{-}RN{-}H + R'{-}CHO \rightarrow RO{-}RN{-}CHR'{-}NR{-}OR + RO{-}RN{-}CHR'{-}OH$$

(1) $R = CH_3$
a) $R' = H$
b) $R' = C_3H_7$

(2a) b.p. 40 °C/30 mm
(2b) b.p. 62 °C/12 mm

(3a) b.p. 50 °C/30 mm
(3b) b.p. 28 °C/12 mm

These new types of hemiacetals can be distilled without decomposition in contrast to the usual *N*-hemiacetals, and do not tend to yield the symmetrical acetals by disproportion-

ation by splitting off aldehyde even when, as in the case of the formaldehyde compound, the b.p. of the hemiacetal *(3a)* is higher than that of the acetal *(2a)*.

With amines, hydrazines, and thiols, the corresponding types of mixed acetal are formed, *viz.* *(4)*–*(7)*, *e.g.* from *(3a)*:

RO–RN–CH_2–NR'_2 *(4)* R = CH_3, R'_2N = piperidine, b.p. 61–62 °C/10 mm

RO–RN–CH_2–NR–NR_2 *(5)* R = CH_3, b.p. 46 °C/12 mm

RO–RN–CH_2–SR' *(6)* R = CH_3, R' = C_4H_9, b.p. 74 °C/10 mm

or from *(3b)*:

RO–RN–CHR'–SR' *(7)* R = CH_3, R' = C_3H_7, b.p. 101 °C/23 mm

The acetals can be split by acyl chlorides, just as *Böhme* and *Hartke* [3] found for aminals, *e.g.*:

(2a) + Ph–CO–Cl → RO–RN–CH_2–Cl + Ph–CO–NR–OR + RO–CO–Cl + RO–CO–NR–OR

Received, May 16th, 1963 [Z 508/339 IE]
German version: Angew. Chem. 75, 640 (1963).

[1] Communication No. 15 on Hydroxylamine Derivatives; Communication No. 14: *G. Zinner*, Arch. Pharmaz. in the press; Communication No. 13: *G. Zinner*, Arch. Pharmaz. *296*, 57 (1963).

[2] Present address: Institut für Pharmazie und Lebensmittelchemie der Universität Münster/Westfalen (Germany).

[3] *H. Böhme* and *K. Hartke*, Chem. Ber. *93*, 1305 (1960).

Isolation of the Diphenylphosphorus Radical

By Doz. Dr. Ulrich Schmidt, Dr. F. Geiger, Dipl.-Chem. Asmus Müller, and Dipl.-Chem. K. Markau

Chemisches Laboratorium der Universität und Institut für Elektrowerkstoffe der Fraunhofer-Gesellschaft, Freiburg/Breisgau (Germany)

Simple organic phosphorus radicals which do not contain other hetero-atoms have not yet been prepared. There were, however, strong indications for their existence, even if short-lived [1].

Using the same practical methods which led to the isolation of the phenylsulfur radical [2], we succeeded in identifying the diphenylphosphorus radical. When evaporating tetraphenyldiphosphine is irradiated with short-wave ultraviolet light at 0.01 mm Hg and the vapor condensed immediately behind the zone of irradiation on a cold finger cooled with liquid nitrogen, diphenylphosphorus condenses as a faintly pink transparent film which loses its color only at 170 °K after 30 min. The diphenylphosphorus radical is therefore equal in thermal stability to arylsulfur radicals substituted by phenyl or by electron donors [3]. In the same way, photolytic cleavage of the P-H bond in diphenylphosphine yields the diphenylphosphorus radical.

Electron spin resonance measurements at 77 °K showed a strong signal with a weakly anisotropic g-factor (g = 2.009).

Received, May 17th, 1963 [Z 506/334 IE]
German version: Angew. Chem. 75, 640 (1963).

[1] For references see *E. Müller, H. Eggensperger*, and *K. Scheffler*, Liebigs Ann. Chem. *658*, 103 (1962).

[2] *U. Schmidt* and *A. Müller*, Angew. Chem. *75*, 299 (1963); Angew. Chem. internat. Edit. *2*, 216 (1963).

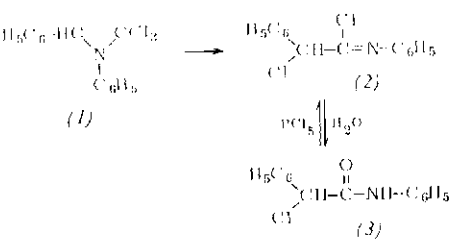
[3] *U. Schmidt, A. Müller*, and *K. Markau*, Tetrahedron Letters, in the press.

Isomerization of 1,3-Diphenyl-2,2-dichloroaziridine

By Professor Dr. H. W. Heine and Amos B. Smith III

Department of Chemistry, Bucknell University, Lewisburg, Pennsylvania (U.S.A.) and Institut für Organische Chemie der Universität Köln (Germany)

Unstable 1,1-dichlorocyclopropanes that quickly isomerize into 2,3-dichloro-1-propene systems have been postulated as intermediates in the reaction of dichlorocarbene with cyclobutene [1] and benzofuran [2]. That 1,1-dihalocyclopropanes can indeed undergo such isomerizations has recently been confirmed by the preparation and thermal conversion of 6,6-dibromobicyclo[3,1,0]hexane into 2,3-dibromocyclohexene [3]. We wish to report the first example of a similar type of isomerization with an aziridine system: 2 g of 1,3-diphenyl-2,2-dichloroaziridine *(1)* [4] was refluxed in 20 ml of toluene for 24 hours, and the toluene was evaporated *in vacuo*. Purification of the product by rapid distillation in micro distillation equipment yielded *N*-phenyl-α-phenyl-α-chloroacetimidoyl chloride *(2)*, b.p. 146–148 °C/0.2 mm. Distillation must be very rapid and the distillation column short in order to prevent charring.



Hydrolysis of the oil gave α-chloro-α-phenylacetanilide *(3)* in 95 % yield; treatment of *(3)* with PCl_5 gave *(2)* plus a slight impurity evidenced by two additional peaks in the infrared spectrum which could not be eliminated by distillation.

The infrared spectrum of *(2)* had an expected absorption band at 1680 cm^{-1}, *i.e.* in the region where imido chlorides absorb, *e.g.* *N*-methylbenzimidoyl chloride has a peak at 1678 cm^{-1}. The band at 737 cm^{-1}, ascribed by *Fields* and *Sandri* [4] to the $\diagdown CCl_2$ group of the dichloroaziridine, is still discernible in the crude acetimidoyl chloride but not in the distilled product. 1,3-Diaryl-2,2-dichloroaziridines rearrange into α-chloro-α-phenylacetanilides in water [4, 5]. Imido chlorides such as *(2)* would be plausible intermediates for this rearrangement.

Received, May 27th, 1963 [Z 513/336 IE]
German version: Angew. Chem. 75, 669 (1963).

[1] Unpublished studies of *E. Vogel* and *H. Kiefer* reported by *E. Vogel*, Angew. Chem. internat. edit. *2*, 1 (1963).

[2] *W. E. Parham, C. G. Fritz, R. W. Soeder*, and *R. M. Dodson*, J. org. Chemistry *28*, 577 (1963).

[3] *J. Sonnenberg* and *S. Winstein*, J. org. Chemistry *27*, 748 (1962).

[4] *E. K. Fields* and *J. M. Sandri*, Chem. & Ind. *1959*, 1216.

[5] *A. G. Cook* and *E. K. Fields*, J. org. Chemistry *27*, 3686 (1962).

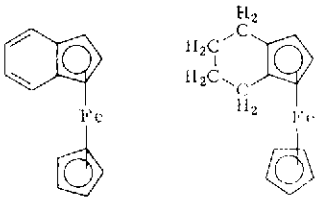
π-Cyclopentadienyl-π-indenyliron (Benzoferrocene)

By Dr. R. B. King and M. B. Bisnette

Mellon Institute, Pittsburgh, Pennsylvania (U.S.A.)

We have obtained benzoferrocene *(1)* as a red-violet stable crystalline solid (m.p. 74–76 °C, subl. ca. 70 °C/0.1 mm) in yields of up to 9 % of pure material by treating iron(II) chloride simultaneously with solutions of sodium indenide and sodium

cyclopentadienide in tetrahydrofuran. The product was separated from the ferrocene also formed in this reaction by chromatography and fractional sublimation.



(1) (2)

The olefinic nature of the two double bonds in the C_6-ring of the indenyl residue in benzoferrocene *(1)* is demonstrated by the absorption of two moles of hydrogen in ethanol solution in the presence of palladium-charcoal to form cyclopentadienyltetrahydroindenyliron (tetrahydrobenzoferrocene) *(2)* as stable orange crystals (m.p. 39–41 °C, subl. ca. 70 °C/0.1 mm). It is of interest that several years ago *Fischer* and *Seus* [1] successfully hydrogenated bis-indenyliron (*s*-dibenzoferrocene) in a similar manner.

Received, May 27th, 1963 [Z 514/337 IE]
German version: Angew. Chem. *75*, 642 (1963).

[1] *E. O. Fischer* and *D. Seus*, Z. Naturforsch. *9b*, 386 (1954).

CONFERENCE REPORTS

Food Chemistry and Forensic Chemistry

The 22nd annual meeting of the South-West German section of the Division of Food and Forensic Chemistry of the Gesellschaft Deutscher Chemiker (German Chemical Society) took place in Mainz (Germany) on April 4th and 5th, 1963.

From the agenda:

Determination of Milk Protein in Meat Products

R. Thalacker, Gießen (Germany)

The detection and quantitative determination of milk protein in meat products is of interest, because addition of not more than 2 % (referred to the meat and fat content) of separated milk protein is allowed in the preparation of certain meat products. *Kutscher*, *Nagel*, and *Pfaff* [1] determined the phosphoprotein-phosphorus of the meat product and so calculated the milk protein content. We used a similar procedure, the differences from the Kutscher method being as follows: the lipids were extracted with alcohol and alcohol/chloroform (instead of alcohol/ether), and acid-soluble phosphorus compounds and nucleic acids were removed by addition of perchloric acid according to the method of *Schneider*, *Hogeboom*, and *Ross* [2]. Phosphoric acid groups were not removed by hydrolysis with sodium hydroxide; the phosphoproteins and tissue proteins were combusted with 60 % perchloric acid. Phosphorus was determined in the combustion solution by the method of *Allen* [3,4].

The phosphoprotein-phosphorus content of meat products containing no milk protein as found by the perchloric acid procedure was 7–15 µg of P per g, representing an apparent milk protein content of 0.1–0.23 % (on the basis of a phosphoprotein-phosphorus content of 0.65 % in milk protein). Similar blank values were reported by *Kutscher* et al. The milk protein determined in unheated sausage meat after deduction of the blank value and on the basis of the known phosphoprotein-phosphorus content of the milk protein was 96–98 % of known additions; in samples heated for 2–3 hours at 100 °C or for 40 minutes at 118 °C, the milk protein found was only 65–70 % of the known additions. It is possible that a portion of the phosphoprotein-phosphorus of the milk protein was hydrolysed to phosphate. *Belec* and *Jenness* [5] reported similar losses of phosphorus after heating sodium caseinate solutions to 110–140 °C; on heating 3 % sodium caseinate for 1 hour at 110 °C, it lost about 20 % and at 120 °C as much as 40 % of its casein phosphorus as inorganic orthophosphate.

[1] *W. Kutscher*, *W. Nagel*, and *W. Pfaff*, Z. Lebensmittel-Unters. u. Forsch. *115*, 117 (1961).

[2] *W. C. Schneider*, *G. H. Hogeboom*, and *H. E. Ross*, J. Nat. Cancer Inst., *10*, 977 (1950).

[3] *R. J. L. Allen*, Biochem. J. *34*, 858 (1940).

[4] *R. Thalacker*, Dtsch. Lebensm. Rundschau *59*, 111 (1963).

[5] *J. Belec* and *R. Jenness*, J. Dairy Sci. *45*, 12 (1962).

The Investigation of Writing Inks in Ball-point Pen Writing Samples

R. Kliffmüller, Siegen (Germany)

Handwritten corrections written with a ball-point pen on a proof motivated chemical investigations of the pertinent types of ink. Extensive literature is available on the examination of conventional writing inks and ink script but ball-point pen colors have been only briefly investigated. Paper chromatography using the "reversed phase" technique was applied for this investigation. The paper was treated with vaseline (2 % white vaseline in petroleum ether; Schleicher & Schüll No. 2043b paper) for the stationary phase, and a mixture of methanol, 15 % ammonia, and ethyl acetate (50:50:2 v/v) was used as mobile phase. After removal from the script, the writing ink was chromatographed by the ascending technique. The two samples were shown to differ in the number and composition of their constituent dyestuffs. Later, 22 commercial ball-point pen inks were investigated. Development with ethanol, 25 % ammonia, and ethyl acetate (50:50:12 v/v) was good for colors other than most blues. The separation of blue colors tended to be streaky, owing to the presence of non-colored interfering substances.

The Detection of Sweetened, Fortified, and Diluted Wines [6]

H. Rebelein, Würzburg (Germany)

Relationships have been found between the original malic acid content (TM), the original sugar content (TA), and the residual quantity of extract after removal of glycerol, butylene glycol, acids, and carbohydrates (RE) of wines, which give characteristic indices. Formulae were developed on a sound theoretical basis for the calculation of TM, TA, and RE. The index values derived from the values of TM, TA, and RE can be used to show whether a wine has been sweetened, fortified with spirit, improved by dilution, or over-diluted. The indices can also show whether a wine can justifiably be called a top-quality product.

The REZ-value $[TA \times (TM/RE)^{3}/_{4}]$ has a mean value of 47. REZ-Values of over 61 generally indicate additions of sugar or spirit.

[6] Cf. Klosterneuburger Mitt. Rebe u. Wein XII A, 227 (1962)

The $\sqrt[3]{f}$-value $\frac{TM - 0.11 \times RE}{(TM/RE)^{1/2} \cdot (RE)^{1/2}}$ has a mean value of 1. $\sqrt[3]{f'}$-Values of less than 0.88 indicate the addition of sweet liquor or water. $\sqrt[3]{f}$-Values of over 1 are found in red wines and top quality wines.

The H-value $\frac{\text{REZ-value}}{(\sqrt[3]{f'}\text{-value})^2}$ is normally of the same order of magnitude as the REZ-value but is considerably greater than the REZ-value in diluted wines and considerably smaller in top quality wines. Wines that are modified in order to taste "natural" can also be recognized even if the REZ-value does not exceed the limit of 61 when the $\sqrt[3]{f'}$-value is low and the H-value is high (over 68).

The relationships found are not dependent on grape variety, vintage, wine-growing district, etc. They have been confirmed so far on ca. 500 (natural, unsugared) wines of 1949 to 1962 vintage and with 100 foreign wines of varying origin.

[VB 698/84 IE]

German version: Angew. Chem. 75, 643 (1963).

Symposium on Starch

The Arbeitsgemeinschaft für Getreideforschung (Society of Cereal Research) and the Bundesforschungsanstalt für Getreideverarbeitung (Federal Research Establishment for Cereal Processing) arranged this year's Starch Symposium in Detmold (Germany) from April 24–26th.

From the agenda:

Investigation on Aqueous Solutions of Natural and Enzymatically Synthetized Amyloses

E. Husemann, Freiburg/Breisgau (Germany)

Natural amylose from potato starch and enzymatically synthetized amylose of the same degree of polymerization differ in that natural amylose undergoes retrogradation from aqueous solutions whereas synthetic amylose does not or only extremely slowly. Furthermore, the degree of polymerization of natural amylose remains almost constant on digestion with β-amylase and phosphorylase, whereas that of synthetic amylose falls off continuously. The lack of uniformity of the two amyloses is great, $M_w : M_n$ for natural amylose is about 2 but for synthetic amylose is less than 1.04. The degree of association was examined by means of light-scattering measurements in water and it was found that about 80 % of the natural amylose is associated, whereas with the synthetic product, only a small proportion of the material formed large aggregates. These results may be explained as being due to the different molecular-weight distributions, since light-scattering and viscosity measurements of a homologous series of polymeric synthetic amyloses show that these have a rising tendency to associate with decreasing degree of polymerization. Moreover, there is a solution gap in aqueous solution between degrees of polymerization of 50 to about 1000. The different behavior of natural and enzymatically synthetized amyloses toward β-amylase and phosphorylase can have different causes. Thus, in the case of natural amylose, a single chain mechanism is simulated, since aggregates and not individual molecules are degraded. According to *D. French*, the average degree of polymerization of a heterogeneous product of $M_w : M_n = 2$ remains constant over a considerable range even during multichain degradation. In addition, the speed of degradation depends on the degree of polymerization itself. The decision as to which of these three possibilities is pertinent was made by degradation experiments on both uniform synthetic amyloses of different degrees of polymerization and mixtures of homogeneous substances. Experiments showed that degradation of even considerably associated uniform substances led to a decrease in the degree of polymerization, so that the first possibility is excluded. In addition, it appeared that even in the case of low heterogeneity of the material of $M_w : M_2 = 1.25$, the degree of polymerization falls only inappreciably, so that the second possibility too cannot suffice as a satisfactory explanation. On the contrary, fractionations of mixtures of synthetic amylose after degradation by β-amylase and phosphorylase showed a clear dependence of the speed of degradation on the degree of polymerization, hence it was concluded that the third possibility was correct and that degradation therefore proceeds by a multichain mechanism for both the synthetic and the natural amylose, the constancy of the degree of polymerization in natural amylose depending on the more rapid fission of the shorter chains.

Influence of γ-Rays on Potato Starch in Relation to its Water Content

A. Guilhot and *H. Reuschl*, Paris (France)

The action of γ-rays (30 mr) on potato starch was investigated in relation to the water content of the starch with particular regard to the degradation of polyglucosidic chains and the formation of oxidation and dehydration products. Hydrolytic fissions appear to take place by intramolecular elimination reactions (formation of glucose in dry starch; presence of hydroxymethylfurfural). The water content of the starch can affect its radiolytic reactions in three ways. One phenomenon is a protective effect against oxidation reactions, which is more pronounced, the less water the starch contains; it is possible that an energy transfer from activated glucose units to water molecules via hydrogen bonds is involved. The second phenomenon is a protective effect against chain splitting reactions, which appears at water contents over 21 %. This effect may depend on a greater mobility of the chain fragments, which favors recombination of the chain fragments. Thirdly, formation of glucose increases with the water content of the starch via transition zones which correspond exactly to individual stages that may be observed at water contents of 10 % on the one hand and of 33 % on the other in the state of compression of the water in the starch. The study of radiolytic reactions of hydrated potato starch may permit conclusions to be drawn concerning its macromolecular structure.

Promotion of Saccharification of Starch by Ultrasonic Waves

M. Samec, Ljubljana (Yugoslavia)

The properties of individual varieties of starch are sometimes changed very considerably by ultrasonic treatment at 14 kcps by undergoing peptization. Comparison of the course of saccharification of maize starch with and without previous ultrasonic treatment has shown that treated maize starches can be saccharified much more quickly and extensively than untreated maize starch. Effective ultrasonic treatment can be undertaken not only with paste but also with starch suspended in cold water, so that the starch grains remain intact and can be separated off easily by settling or centrifuging.

Selective Catalytic Oxidations of Carbohydrates as a Means of Constitutional and Conformational Analysis

K. Heyns, Hamburg (Germany)

Methods for catalytic oxidation or dehydrogenation using platinum catalysts with oxygen or air also permit selective

dehydrogenation of polyhydroxy compounds and carbohydrate derivatives in aqueous solution or in organic solvents. Primary hydroxyl groups are oxidized faster than secondary hydroxyl groups and, depending on the type of substrate, carboxylic acids, aldehydes, or ketones are formed. The method was applied to secondary hydroxyl groups in cyclitols such as inositol. It was found that axial hydroxyl groups are dehydrated specifically, equatorial groups are not attacked. The dependence on configuration and conformation was also demonstrated on the basis of the behavior of the condoritol isomers *i.e.* tetrahydroxycyclohexanes, some of which occur in nature and which also contain a C_6-ring. These compounds exist in a semi-chair conformation. A more recent development of the method of selective hydrogenation of axial hydroxyl groups was applied to pyranose rings, using appropriately glucosidically blocked derivatives of the pyranose forms of arabinose, ribose, lyxose, and xylose. The investigations have shown that selective catalytic oxidation at platinum surfaces yields information on the conformative behavior of pyranoses in aqueous solution. Finally, these conditions were also illustrated for each of the possible 1-C- or C-1-forms, and the previous experimental findings with methylpentoses and hexoses, especially glucose and galactose, were discussed.

[VB 703/86 IE]

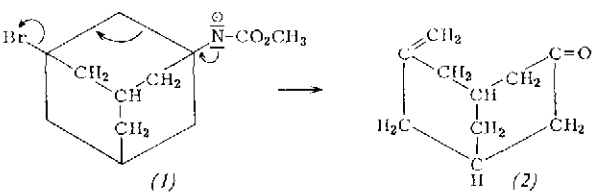
German version: Angew. Chem. *75*, 689 (1963).

SELECTED ABSTRACTS

Investigations of radioactive clouds in the upper atmosphere were carried out by *E. Keppler* and *G. Pfotzer*. In the latter half of October, 1962, measurements of the radioactivity at heights between 16 and 25 km were made over the West Harz (Germany) by counting tubes carried in high-altitude balloons and showed counts which were sometimes many times greater than the normal value originating from cosmic rays. The additional radioactivity detected in this way appeared to be localized in one or more layers at relatively sharply-defined heights in the upper atmosphere. The results were interpreted as being due to radioactive clouds originating from the atomic bomb explosions in Novaya Semlya. The highest value was measured on October 22nd, 1962. The activity in the cloud was estimated at 10^{-6} Curie/m³ and was the highest activity found so far at great heights. Naturwissenschaften *50*, 220 (1963) / –Sn. [Rd 588/161 IE]

The association of the hydroxyl groups in liquid water was examined by *W. Luck*. Using an approximation method, the fraction of free (*i.e.* not hydrogen-bonded) OH groups in water was determined from the temperature dependence of the infrared absorption bands. The relative proportion of free OH groups can be calculated precisely, and is about twice as large at 80 °C as at 0 °C. From the fraction of free OH groups at 0 °C (about 10 %) calculated on the basis of energy considerations, an absolute scale can be obtained, which seems to agree well with the infrared measurements. The values calculated for non-associated OH groups by this approximation method are in a surprisingly good agreement with those estimated by *Haggis*, *Hasted*, and *Buchanan* [1] from measurements of the dielectric constant. Water is supposed either to consist of a variety of small aggregates similar to solutions (*Eucken*) or to exist in the form of a partially melted ice lattice (*Bernal* and *Fowler*). The values found for the fraction of free OH groups are far too small to confirm the existence of mostly smaller aggregates. According to the infrared spectra obtained, aggregates of this kind would be required to have unusually high degrees of association. They can be regarded as estimates of the cybotactic groups. / Ber. Bunsenges. physik. Chem. *67*, 186 (1963) / –L. [Rd 560/152 IE]

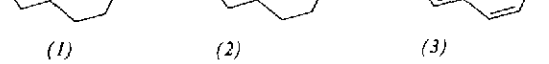
A fragmentation in the adamantane series has been reported by *H. Stetter* and *P. Tacke*. *N*-[3-bromoadamant-1-yl]-methylurethane *(1)*, prepared from 3-bromoademantane-1-carboxamide by Hofmann degradation, was converted smoothly into 3-methylenebicyclo[1,3,3]nonan-7-one *(2)* by treatment with alkali. Ozonolysis of *(2)* afforded bicyclo-[1,3,3]nonandi-3,7-one which was converted into 1,3-dihydroxy-2-nitroadamantane by aldol condensation with nitromethane. Reduction of the diketone with lithium aluminum hydride gave bicyclo[1,3,3]nonan-3,7-diol, from which the previously unknown compound 2-oxa-adamantane



(1) *(2)*

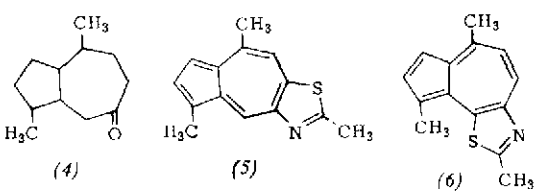
can be prepared by intramolecular dehydration. / Chem. Ber. *96*, 694 (1963) / –T. [Rd 561/153 IE]

Thiazoloazulenes have been prepared by *G. Fischer* and *E. J. Poppe*. The octahydro-compound *(2)* was obtained from bicyclo[5,3,0]decan-8-one *(1)* by bromination and heating the resultant bromoketone with thioacetamide. Dehydrogenation of *(2)* with sulfur in decalin afforded 2'-methylthiazolo[4',5':1,2]azulene *(3)* as blue-black prisms, m.p. 139 °C.



(1) *(2)* *(3)*

Its visible spectrum (λ_{max} = 608 mμ) is very similar to that of 1,2-benzazulene. The thiazoloazulenes are much weaker bases than the thiazoles. (–)2,8-Dimethylbicyclo[5,3,0]-decan-5-one *(4)* was converted analogously into the isomers *(5)* and *(6)*, the structures of which are highly likely to be



(4) *(5)* *(6)*

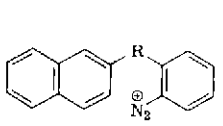
those given because of the similarity of their spectra with those of 5,6- and 4,5-benzazulene, respectively; *(5)* forms blue-violet needles, m.p. 85.5–86 °C; *(6)* also forms violet-blue needles, m.p. 146–148 °C. Compounds *(5)* and *(6)* had already been prepared by *Treibs* and *Hiebsch* [1]. / Z. Chem. *3*, 26 (1963) / –Kr. [Rd 562/154 IE]

A study of intramolecular arylations in the naphthalene series led *R. Huisgen* and *W. D. Zahler* to conclude that cyclization reactions of the type of the Pschorr phenanthrene synthesis can occur by both ionic and radical mechanisms. With *(1)*, R = CO, angular cyclization giving *(2)* is preferred to linear cyclization giving *(3)* by a factor of 2.4 for electrophilic arylations and of 9.5 for radical substitution. For the ionic

[1] J. chem. Physics *20*, 1452 (1952).

[1] *W. Treibs* and *J. Hiebsch*, unpublished work.

mechanism, the ratio *(2)*:*(3)* depends on the bridging group R = O: 2.5; CO: 2.4; N CH_3: 1.3; CH_2: 1.0. This lack of selectivity cannot be reconciled with normal electrophilic



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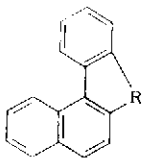

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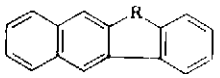
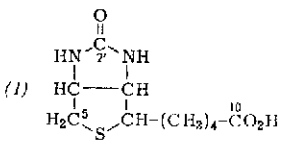


(3)

naphthalene substitution. The authors postulate a hydride bridged cation as intermediate. / Chem. Ber. *96*, 736, 747 (1963) / –Z. [Rd 563/155 IE]

The mode of biosynthesis of biotin was elucidated by *A. Lezius*, *E. Ringelmann*, and *F. Lynen* by culture of *Achromobacter IV S* on a medium containing isovaleric acid, to which $^{14}CO_2$



(1)

and [3-^{14}C]cysteine were added, and by degradation of the biotin *(1)* formed. Incorporation of the radiocarbon, derived from the $^{14}CO_2$ occurred at the position of the urea-carbonyl (C-2') and the carboxyl group (C-10) of *(1)*, and that from the [3-^{14}C]cysteine at C-5 of *(1)*. It is assumed that *(1)* is synthetized from cysteine, pimelyl-CoA, and carbamyl phosphate. Pimelyl-CoA arises (analogous to the synthesis of fatty acids) from 3 moles of malonyl-CoA. / Biochem. Z. *336*, 510 (1963) / – De. [Rd 566/156 IE]

Crystalline isoenzymes of lactic dehydrogenase (LDH) from human organs were investigated by *E. D. Wachsmuth* and *G. Pfleger*. They obtained the pure isoenzymes from kidneys, heart muscle, and brain by extraction of the homogenized tissue, centrifugation at 2200 g, precipitation at pH 4.85 with acetic acid, addition of Ca phosphate gel (pH 7.2) and re-elution with M/3 phosphate buffer, and repeated precipitation with ammonium sulfate to give crude crystals, which were dialysed at pH 7.2 against M/30 phosphate buffer, transferred to a Sephadex column, and eluted by a sodium chloride gradient. The isoenzyme fractions (I–V) were recrystallized 5–6 times with ammonium sulfate. The following isoenzymes were obtained pure (specific activities in brackets): from brain I–III, from kidney I and II, and from heart I and II (I: 35000, II: 40000, and III: 53000; from heart at 37 °C: I: 82000, II: 92000). Isoenzymes of the same charge (electrophoresis) from various other organs gave similar results, *e.g.* in the determination of substrate-dependence, inhibition by sulfate ions, and the pH-dependence of the enzyme action, temperature coefficients, and heat stability. / Biochem. Z. *336*, 545 (1963) / –De. [Rd 567/157 IE]

BOOK REVIEWS

Anorganische Chemie (Inorganic Chemistry) by *I. Náray-Szabó*, translated into German by *A. Beliczay*. Vol. I and Vol. II. Akademie-Verlag, Berlin 1959 and 1962. 1st Edit., Vol. I: 664 pp., 34 illustr., Vol. II: 813 pp., 22 illustr., both volumes cloth-bound, tog. DM 97.– (about $25.–).

Volumes I and II of the three-volume work "Anorganische Chemie" are now available in a German translation. The general section of the first volume is concerned with atomic structure, nuclear chemistry, and the basic features of chemical bonding. In the specialized section of this volume, the chemistry of the non-metallic elements (hydrogen, halogens, chalcogens, nitrogen and carbon groups, and boron) is dealt with. The second volume describes the chemistry of the metals in main groups 1 and 2, aluminum, and the transition metals in groups 3 to 7 of the periodic table. The discussion of the remaining elements and their compounds is intended for the third volume.

The author treats the very extensive subject-matter mostly descriptively and dispenses almost completely with the presentation of theoretical and systematic aspects in favor of an extremely exhaustive account of the chemical and physical properties of the elements and compounds. Hence "Anorganische Chemie" tends more to breadth than depth in approach and is more in the nature of a reference work than a text-book. It also contains numerous misprints and errors of nomenclature which will not be dwelt on here. With future editions in mind, however, some of the frequently recurring inaccuracies should be mentioned. For instance, the difference between oxidation number and the number of bonds formed ought to be made clear when "valency" is being considered; complex ions such as $[NH_4]^+$, $[SO_4]^{2-}$, and $[AlF_6]^{3-}$ ought not to be called "radicals", and the valency "dash" ought to be reserved exclusively for the representation of an electron-pair bond, so that obsolete formula representations such as Na–N=N≡N can be avoided.

The aim of the author, as stated in the preface, to provide "a small handbook of inorganic chemistry" has undoubtably been attained. Unfortunately, its value is impaired by the fact that the author almost invariably gives no references to original papers and limits himself to the available hand- and text-books, encyclopaedias, and monographs, in which the most recent literature usually has not been considered. Nevertheless, this book by *Náray-Szabó* does have an abundance of experimental and physical data and is therefore useful as a reference book for preliminary orientations; in this connection, a carefully planned subject and formula index facilitates rapid location of any chosen compound. From this aspect, it can be recommended to all who are interested in a handy reference book.

R. Nast [NB 31/50 IE]

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Production of Polyhydric Alcohols from Wood Polysaccharides

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By hydrolysis and hydrogenolysis, plant polysaccharides, i.e. mainly cellulose and hemicelluloses, can be converted with high yields into polyhydric alcohols (hexitols, pentitols, glycerol, ethylene glycol, propylene glycol). Procedures which have been developed in the U.S.S.R. are described. Of particular interest is the simultaneous hydrolysis and hydrogenolysis of plant polysaccharides with noble metal catalysts. Here yields are almost quantitative.

1. Introduction

Wood matter, *i.e.* the cell walls of annual and perennial plants, is to be considered together with oil and coal as a major raw material for the chemical industries. Wood has the advantage over mineral raw materials that it is renewed annually.

Every year, millions of tons of woody waste materials are produced throughout the world in the form of wood-processing residues, straw from cereals, corn cobs, cottonseed husks, *etc.* These wastes were not used up efficiently until now.

During the last 15–20 years, a highly developed hydrolysis industry has been built up in the U.S.S.R. This industry is based on the transformation of cell-wall polysaccharides into the corresponding monosaccharides, which are then subjected to chemical and biochemical treatment to produce ethyl alcohol, furfural, glucose, and other commercially important compounds. During the last ten years, as a result of numerous scientific investigations, procedures have been developed in our country for the production of polyhydric alcohols from monosaccharides obtained by hydrolysis of various vegetable wastes, which are of great practical and theoretical interest.

Here a short summary is given of the work carried out by Soviet scientists in this field.

2. Cellulose and Hemicelluloses

Plant cell wall polysaccharides consist mainly of cellulose and hemicelluloses.

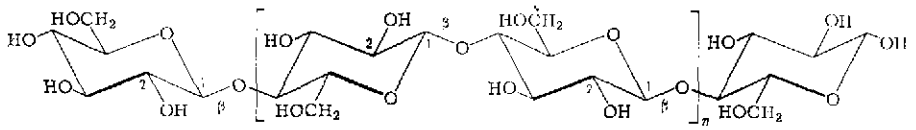
Cellulose is a stereoregular linear polymer built up from β-D-glucose residues. On quantitative hydrolysis of cellulose, D-glucose is formed and can be converted into sorbitol, a hexahydric alcohol, by reduction with hydrogen.

Hemicelluloses consist of mixtures of complex polysaccharides, *viz.* arabinoxylouronides, glucomannans, or glucomannogalactans. Large amounts of arabinogalactans are also present in larch wood. Hydrolysis of these polysaccharides yields monosaccharides or monosaccharide mixtures containing xylose, arabinose, mannose, glucose, galactose, and acidic products, consisting mainly of aldobiuronic acids.

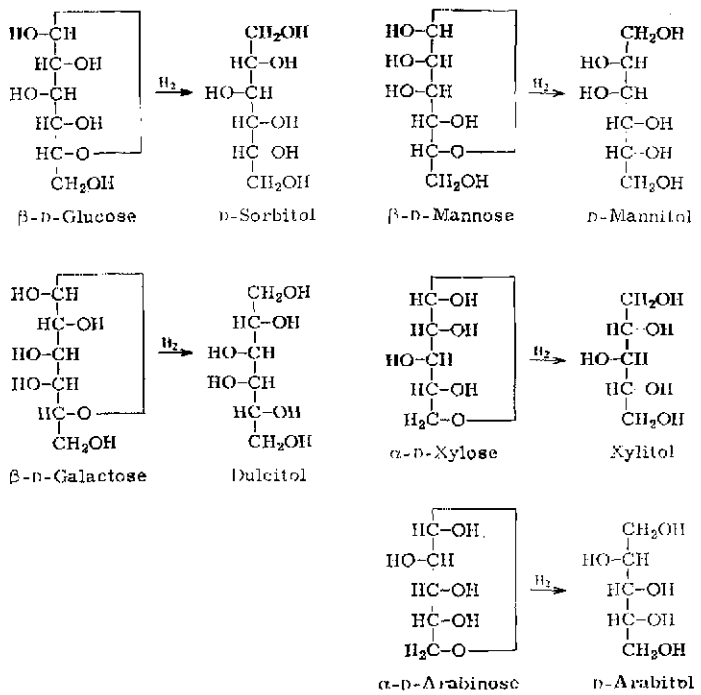
Depending on the nature of the vegetable matter used, the hemicelluloses contain different ratios of the above monosaccharides. By careful selection of the vegetable raw material and the hydrolysis conditions, hydrolysates can be obtained that contain predominantly one specific monosaccharide. For example mild hydrolysis of cottonseed husks or corn cobs gives hydrolysates with monosaccharides containing 85–90 % D-xylose. Hydrolysis of the hemicelluloses from the outermost layers of spruce or pine trunks gives a monosaccharide mixture

with about 60 % mannose. In the pulping of fir wood, the latter is subjected to an extraction with hot water prior to the cook in order to remove arabinogalactan. The latter can be hydrolysed further to form a monosaccharide mixture containing about 90 % galactose.

On mild hydrogenation of such hydrolysates, mixtures of polyhydric alcohols are obtained. Depending on the constitution of the original vegetable raw material, these consist chiefly of sorbitol, xylitol, dulcitol, or mannitol.



Cellulose



by hydrolysis of plant tissue polysaccharides. Hydrogenation of pure monosaccharides with hydrogen and a nickel catalyst in aqueous solution offers no difficulties. However, hydrogenation of impure monosaccharides involves the problem of rapid catalyst contamination. Thus, special methods had to be developed to eliminate proteins, tannins, pectins, and mineral constituents from the vegetable raw materials. The means of purification depends on the sort of raw material used; it consists mainly in combined treatment with hot water and cold dilute mineral acid.

The purified raw material is then hydrolysed. The conditions used again depend on the type of raw material in question. For instance, after the purification pretreatment, cottonseed husks and corn cobs [1, 2] are subjected to two-stage hydrolysis (Fig. 1). In the first stage, the pentosans are hydrolysed by heating the desintegrated raw material with 0.5 N sulfuric acid at 120 °C. The pentose hydrolysate obtained is separated from insoluble lignocellulose. The latter is then hydrolysed in the second stage; however this cellulose hydrolysis offers some difficulties, and hence the four following processes are applied in the U.S.S.R.

α) Lignocellulose is hydrolysed with dilute sulfuric acid by a method involving combined vertical and horizontal percolation [4]. This process is performed in special hydrolysers with 0.5–0.8 % sulfuric acid for 2–3 hours at 170–190 °C. The yield of glucose is about 60–70 % of the cellulose content. The glucose content in the hydrolysates generally does not exceed 2.5–3.5 %.

β) The hydrolysis of wood lignocellulose is effected with 41 % hydrochloric acid in a battery of hydrolysers at room temperature. The hydrolysate contains 15–18 % carbohydrates and 27–30 % HCl. After recovery of the HCl by means of multistage evaporation of the hydrolysate, the aqueous solution of glucose is subjected to inversion with hot dilute hydrochloric acid; the glucose solution may then be hydrogenated directly, or else crystalline glucose is first recovered via its adduct with sodium chloride by means of the method of *Lebedev* and *Liubin* [5], and then hydrogenated.

3. Procedures for Producing Polyhydric Alcohols from Polysaccharides

The conversion of wood polysaccharides into the corresponding polyhydric alcohols may be achieved by the following principal methods:

a) Hydrolysis of the polysaccharides to monosaccharides and subsequent hydrogenation of the latter to polyhydric alcohols;

b) Simultaneous hydrolysis and hydrogenation of the polysaccharides;

c) Hydrogenolysis of the hexitols and pentitols obtained by a) or b) to glycerol, ethylene glycol, and propylene glycol;

d) Pyrolysis of the cellulose to give levoglucosan.

a) Hydrolysis of Polysaccharides and Hydrogenation of the Monosaccharides

At present, the best studied and the most familiar process is the hydrogenation of monosaccharides produced

[1] *A. Ya. Kolossova* and *Z. M. Potegaylo:* Purification and pentose hydrolysis of corn cobs, Gidrolisn. i Lesokhim. Prom. *13*, No. 6, p. 8 (1960).

[2] *A. Ya. Kolossova, Yu. N. Burkovskaya, A. N. Gladkova,* and *N. S. Maksimenko:* Two-stage hydrolysis of corn cobs, Gidrolisn. i Lesokhim. Prom. *13*, No. 8, p. 12 (1960).

[3] *M. E. Shpuntova, E. E. Schneider,* and *S. V. Chepigo:* Usbek. chem. J. *3*, 81 (1958).

[4] *I. I. Korolkov, B. M. Saitsev, V. I. Sharkov, A. S. Vainer, N. I. Efros,* and *N. I. Bubnova:* Percolation hydrolysis with an alternating liquid stream, Gidrolisn. i Lesokhim. Prom. *14*, No. 2, p. 10 (1961).

[5] *G. I. Gorokhov* and *N. V. Korsakov:* Food glucose recovery from wood, Gidrolisn. i Lesokhim. Prom. *13*, No. 5, p. 26 (1960).

γ) The plant tissue or lignocellulose is hydrolysed with concentrated sulfuric acid. This method was developed by *Odintsov*, *Kalnina*, *Chepigo*, and others [6–8] and is applied in different versions, which consist mainly in preliminary wetting of the dry lignocellulose with 100 to 200 kg of 78–80 % sulfuric acid per ton of dry lignocellulose at 50 °C. The mixture is then milled between rollers or in a vibrating mill, left standing at room temperature, diluted with water or hydrolysate, and inverted at 100–120 °C to glucose (cf. Fig. 1).

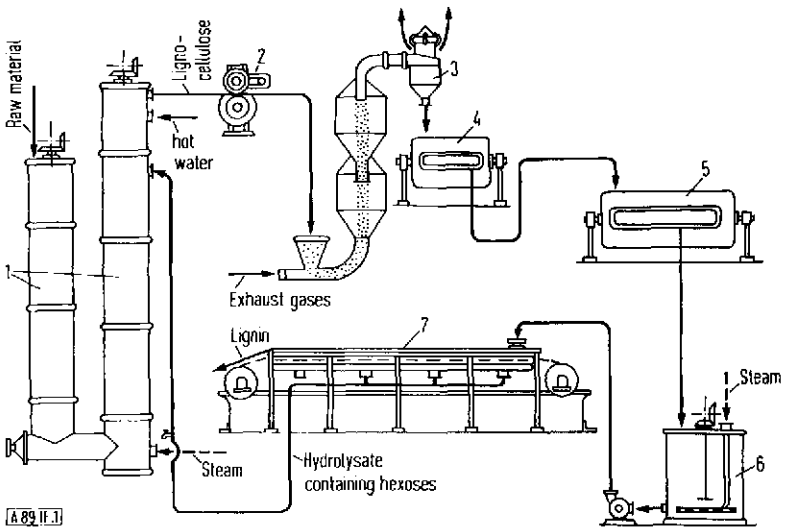


Fig. 1. Flow-sheet for two-stage hydrolysis of plant polysaccharides (after [3])
1: Pentosan hydrolyser
2: Lignocellulose filter
3: Drier
4: Ball-mill
5: Heated ball-mill
6: Invertor
7: Vacuum filter

δ) A mechano-chemical method for processing plant raw materials or lignocellulose was developed by *Levanova*, *Chalov*, and *Sharkov* [9, 10] and involves conversion of the cellulose into an easily hydrolysable form by energetic desintegration in an atmosphere of gaseous hydrogen chloride at elevated temperatures. This treatment degrades the cellulose macromolecules into fragments with 2–5 glucose residues. These cellulose oligomers are soluble in cold water and readily hydrolysed to glucose by dilute hydrochloric acid at 100–120 °C.

Methods β) δ) give glucose yields of 90–95 % of the theoretical amount and provide solutions with 10 to 20 % glucose.

The pentose hydrolysates obtained after separation of the lignocellulose contain 5–12 % dissolved sugars but cannot be hydrogenated directly owing to the presence of some incompletely hydrolysed polysaccharides which inhibit the sugar hydrogenation. These hydrolysates are therefore subjected to further mild hydrolysis until all the dextrins have disappeared from the solution.

The monosaccharide solutions obtained contain mineral acid and other impurities which have to be removed before hydrogenation. Formerly this was effected by neutralization, treatment with activated charcoal, and elimination of mineral impurities with cation and anion exchange resins. Nowadays this process is simplified; the acid is removed with ion-exchange resins, and clarification of the aqueous monosaccharide solutions is effected with activated charcoal [11].

The acid-free aqueous monosaccharide solutions with 9.5–9.7 % dry matter content are then adjusted to pH 7.2–8.9 with sodium hydroxide, heated to 125 °C, and hydrogenated with hydrogen at 60–150 atm in continuous digesters filled with skeleton nickel catalyst. The aqueous solutions of xylitol, sorbitol, and dulcitol obtained are purified over ion-exchange filters and then evaporated to 75–90 % dry content [12].

b) Simultaneous Hydrolysis and Hydrogenation of Polysaccharides

The method of simultaneous hydrolysis and hydrogenation of wood polysaccharides developed recently by *Balandin*, *Vassiunina*, and *Chepigo* [13–18] is of great theoretical interest.

[6] *P. N. Odintsov*, *I. I. Beinerst*, and *N. F. Murashchenko:* Cellulose hydrolysis with small quantities of concentrated sulfuric acid, Gidrolisn. i Lesokhim. Prom. *13*, No. 6, p. 6. (1960).

[7] *E. E. Schneider*, *M. E. Shpuntova*, and *C. V. Chepigo:* A combined method of corn cobs hydrolysis with concentrated sulfuric acid, Gidrolisn. i Lesokhim. Prom. *13*, No. 7, p. 1 (1960).

[8] *P. N. Odintsov*, *A. I. Kalnin*, *V. K. Kalnina*, *S. V. Chepigo*, *E. E. Schneider*, and *M. E. Shpuntova:* Hydrolysis of vegetable substances with concentrated sulfuric acid, Gidrolisn. i Lesokhim. Prom. *14*, No. 3, p. 1 (1961).

[9] *V. I. Sharkov*, *I. I. Korolkov*, and *E. N. Garmanova:* Increase of sugar yield in wood hydrolysis by preliminary milling, Gidrolisn. i Lesokhim. Prom. 9, No. 1, p. 6 (1956).

[10] *V. I. Sharkov* and *V. P. Levanova:* Mechanical-chemical method of transforming cellulose into an easily hydrolyzable state, Gidrolisn. i Lesokhim. Prom. *13*, No. 1, p. 5 (1960).

[11] *E. R. Leikin* and *S. M. Gutina:* Studies of processes for evaporating xylose solutions, Gidrolisn. i Lesokhim. Prom. *14*, No. 5, p. 11 (1961).

[12] *S. V. Chepigo:* Hydrolysis industry's participation in the solution of the tasks of heavy chemistry, Khim. Prom. *1960*, No. 3, p. 1.

[13] *N. A. Vassiunina*, *A. A. Balandin*, *B. I. Korzhev*, *B. Ya. Rabinovitch*, *S. V. Chepigo*, *E. S. Grigorian*, and *R. L. Slutsky:* Recovery of glycerol and glycols by hydrogenation of xylitol, Khim. Prom. *1962*, No. 2, p. 6.

[14] *A. A. Balandin* and *N. A. Vassiunina:* Selective hydrogenation of monosaccharides and polyhydric alcohols, Dokl. Akad. Nauk SSSR *117*, 84 (1957).

Hydrolytic hydrogenation of polysaccharides is performed in acidic medium in the presence of a ruthenium catalyst at elevated temperatures and pressures. At the high temperatures used the dilute acid hydrolyses the polysaccharides to the corresponding monoses, which are rapidly converted into the corresponding polyhydric alcohols in the presence of the hydrogenating catalyst and hydrogen. Almost quantitative yields of polyhydric alcohols are obtained directly from polysaccharides such as cellulose.

The reactions probably go so well because in an acidic medium at high temperatures, monosaccharides are much less stable than the corresponding polyhydric alcohols or their anhydrides, which are also formed under the reaction conditions used.

Barium sulfate or charcoal are used as carriers for the ruthenium catalyst. Optimum conditions for wood cellulose hydrogenation are: 0,7 % phosphoric acid, 160 to 165 °C, 60–80 atm hydrogen pressure, and a reaction time of 50–60 minutes. More drastic reaction conditions lead to degradation products and anhydride formation. At lower hydrogen pressures (40 atm), all other conditions remaining unchanged, the hydrogenation is slowed down; increase of the pressure to 120 atm does not markedly affect the rate of hydrogenation.

For sorbitol recovery from cellulose, phosphoric or hydrochloric acid is required. In the presence of 0.5 % sulfuric acid (based on the amount of solution) hydrolytic hydrogenation proceeds within 30–40 minutes at 150–155 °C; however, besides sorbitol, 25–40 % sorbitan is produced. On increasing the reaction period and raising the sulfuric acid concentration up to 0.8 % at 180 °C, only sorbitan is obtained. Hence sorbitan can be produced directly from cellulose by this method. When phosphoric or hydrochloric acid is used, sorbitol yields of 92–96 % (based on original cellulose) are obtained. When spruce wood hemicelluloses were isolated by alkaline extraction and subjected to hydrolytic hydrogenation in the presence of 0.1 % ruthenium in 0.1 % sulfuric acid at 155–160 °C and 70 atm of hydrogen for 1 hour, polyhydric alcohols were obtained in 78 % yield.

The ruthenium does not dissolve in the hot acidic medium. Similar results were obtained with palladium. Nickel catalysts are not suitable as they dissolve rapidly in hot dilute acids.

Interesting results have been obtained recently from direct hydrolytic hydrogenation of wood. In experiments carried out by *Balandin, Vassiunina, Chepigo*, and *Barysheva* [19] spruce saw-dust was extracted with acetone to remove resins and then hydrolytically hydrogenated in the presence of 0.7 % aqueous phosphoric acid and 0.5 % ruthenium (based on the weight of wood) on a charcoal carrier at 160–170 °C for 45–60 minutes with an initial hydrogen pressure of 30–50 atm.

Lignin and the catalyst were filtered off from the colorless reaction product, the phosphoric acid was removed by anionic exchange resins, and the solution evaporated *in vacuo*. The residue crystallized. The yield of pentitols and hexitols was 95 % based on the weight of original wood polysaccharides.

The lignin was heated with a ruthenium catalyst in the same digester for 2.0–2.5 hours with 1.5 % sodium hydroxide at 50–70 atm hydrogen pressure and 280 to 320 °C. The colorless reaction product turned brown in air and had an intense phenolic odor. On acidification of the solution, no lignoacids and no hydrocarbon layer could be detected. Phenol, *m*-cresol, and pyrocatechol were detected by paper chromatography. The total yield of phenols was 35 % based on the weight of lignin. The ruthenium catalyst sinks to the bottom of the reactor and can be fully recovered.

c) Hydrogenolysis of Monosaccharides to Glycerol, Ethylene Glycol, and Propylene Glycol

The process for the recovery of glycerol, propylene glycol, and ethylene glycol from the polysaccharides of plant tissues involves a series of operations. First the polysaccharides are hydrolysed to monosaccharides by one of the methods mentioned above. Then the monosaccharides (pentoses, hexoses, or their mixtures) are subjected to hydrogenation with hydrogen on a nickel catalyst in an aqueous medium at pH 10 and 220–240 °C and a hydrogen pressure of 150 atm. It is known that under such conditions, a mixture of glycerol and propylene glycol is formed from sorbitol, and that glycerol, ethylene glycol, and propylene glycol are recovered from xylitol. The relative amounts of these products depend on the operating conditions.

Systematic research of this process carried out in the U.S.S.R. has shown that hydrogenation of monosaccharides can yield a mixture containing 35–40 % glycerol, 30–35 % propylene glycol, and 30 % unreacted polyhydric alcohols. The latter can be isolated from the mixture and rehydrogenated. Methanol, ethanol, n-propanol, and erythritol are also formed in small amounts (1–4 %).

The yield of glycerol can be increased to 60 % (based on the weight of original carbohydrates) by repeated hydrogenation of the unreacted pentitols and hexitols.

The mixture of polyhydric alcohols obtained in this way closely resembles commercial glycerol and may be used as a substitute for it in some cases. When a separation of the hydrogenation products is required, this can be

[15] *S. V. Chepigo, A. A. Balandin, N. A. Vassiunina*, and *A. P. Sergeyev:* Production of polyhydric alcohols by catalytic transformations of plant polysaccharides, Khim. Nauka i Prom. *2*, 416 (1957).

[16] *A. A. Balandin, N. A. Vassiunina, S. V. Chepigo*, and *T. S. Barysheva:* Hydrolytic hydrogenation of cellulose, Dokl. Akad. Nauk SSSR *128*, 941 (1959).

[17] *A. A. Balandin, N. A. Vassiunina, G. S. Barysheva*, and *S. V. Chepigo:* Catalytic hydrogenation of polysaccharides, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1957*, 392.

[18] *V. I. Sharkov* and *V. P. Levanova:* Mechanical-chemical method of transforming cellulose into an easily hydrolyzable state, Gidrolisn. i Lesokhim. Prom. *13*, No. 1, p. 5 (1960).

[19] *N. A. Vassiunina, A. A. Balandin, S. V. Chepigo*, and *T. S. Barysheva:* Catalytic hydrogenation of wood and other plant materials, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1960*, 1522.

achieved by rectification [20, 21]; ethylene glycol and propylene glycol are first distilled off under reduced pressure (10 mm Hg), and the glycerol is then recovered with superheated steam and an inert gas. The residue consists of pentitols and hexitols and is recycled for rehydrogenation.

Investigations carried out by *Vassiunina, Balandin, Karguiev* et al. [13] have shown that under suitable hydrogenation conditions, maximum yields of up to 40 % glycerol or up to 44 % propylene glycol can be recovered from xylitol. In these experiments, the nickel catalyst was applied in the form of a finely dispersed powder suspended in the solution. Rapid reaction with rupture between C-3 and C-4 and with the formation of by-products by rupture at other parts of the carbon chain is ensured by thorough stirring of the solution during the hydrogenation.

In investigations by *Sharkov, Bolotova,* and *Oulianovskaya* [22], glycoside formation from monosaccharides and polyhydric alcohols was used to obtain high molecular-weight glucosides in the form of straight chains with many hydroxyl groups. For instance, dehydration in the presence of sulfuric acid yielded glucosides of glycerol, ethylene glycol, xylitol, and sorbitol. The glucose can be replaced by other monosaccharides, *e.g.* xylose, arabinose, galactose, mannose, *etc.* Suitable polyhydric alcohols include mannitol, arabitol, dulcitol, propylene glycol, diethylene glycol, *etc.* By suitable polyhydric alcohol/monosaccharide combinations we were able to obtain glycosides with varying viscosities in solution, varying hygroscopicities, *etc.* In this work, diglycosides were also obtained which contained one molecule of polyhydric alcohol to every two molecules of monosaccharide.

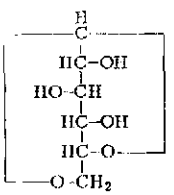
d) Formation of Levoglucosan from Cellulose

A series of investigations by *Golova, Epstein, Odintsova* et al. [23–27] on the recovery from cellulose of glucose anhydride or levoglucosan, which can also be considered as a polyhydric alcohol, is also noteworthy. *Pictet* was the first to obtain this product, which for many years had only theoretical value. At present, levoglucosan is being investigated in the U.S.S.R. as a potential cheap raw material for the chemical industry.

Systematic research has shown that levoglucosan yields of up to 60 % (based on cellulose) can be obtained by stringent observance of suitable reaction conditions.

It was shown, for instance, that the normal conditions of reaction, *i.e.* temperature, pressure, *etc.*, have a less decisive influence on the degradation of the polysaccharide than the physical structure of the polymer and the composition of mineral matter present.

It has been established that pure, closely packed crystalline regions are degraded on heating principally by rupture of β-1,4-glucoside bonds and not of C–C-bonds. Thus, the main product is glucose anhydride (levoglucosan or β-1,6-anhydro-α-1,5-glucopyranose).



Levoglucosan

Thermal degradation of amorphous cellulose yields much less levoglucosan and far more solid, liquid, and gaseous products resulting from more drastic degradation of the cellulose. It was shown experimentally that native cellulose can be used for producing levoglucosan provided its amorphous regions are separated off before hand by mild hydrolysis. The lignocellulose obtained after removing hemicelluloses from lignified plant tissues may also be used.

The yield of levoglucosan is strongly reduced in the presence of some salts, mainly salts of monovalent metals and particularly chlorides. The presence in cellulose of 0.04–0.08 % sodium chloride reduces the yield of levoglucosan from thermal degradations to as low as 10 %. On desalting to a concentration of 3×10^{-4} %, the yield of levoglucosan is increased to 50 to 55 % (based on original cellulose). The salts seem to act as catalysts causing C–C bonds to rupture.

It has also been shown that in order to obtain high yields of levoglucosan, reduction of the pressure to 100 mm Hg is sufficient. The levoglucosan vapors can be removed from the reaction vessel with a stream of inert gas or steam.

Conclusion

This short review shows that it is possible to obtain polyhydric alcohols with different structures and various properties by suitable chemical treatment of the plant polysaccharides.

Utilization of these alcohols as raw materials in various branches of the chemical, textile, food, and pharmaceutical industries is continuously expanding.

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German version: Chemie-Ing.-Techn. *35*, 494 (1963).

[20] *B. N. Balakhontseva* and *N. I. Galperin.* Separation of polyhydric alcohol mixtures, Khim. Prom. *1962*, No. 2, p. 2.

[21] *N. A. Vassiunina, A. A. Balandin, Yu. Mamatov,* and *L. M. Pustovaya:* Quantitative determination of polyhydric alcohols in their mixtures, Gidrolisn. i Lesokhim. Prom. *15*, No. 1, 18 (1962).

[22] *V. I. Sharkov, R. I. Oulianovskaya,* and *A. K. Bolotova:* Glucosides of polyhydric alcohols as substitutes for glycerol, Transactions of the State Research Institute of Wood Saccharification *9*, 138 (1961).

[23] *O. P. Golova, Ya. V. Epstein, V. N. Sergeyeva, A. I. Kalnins, K. N. Odintsov, N. S. Maksimenko,* and *V. G. Panassiuk:* A new method of complex chemical treatment of plant tissues. Gidrolisn. i Lesokhim. Prom. *14*, No. 7, p. 4 (1961).

[24] *O. L. Golova, A. M. Pakhomova,* and *E. A. Andriyevskaya,* Dokl. Akad. Nauk SSSR *112*, No. 3 (1957); *116*, No. 3 (1957).

[25] *O. P. Golova, R. G. Krylova,* and *I. I. Nikolayeva,* Vysokomolekul. Ssoedin. *1*, No. 9 (1959).

[26] *O. P. Golova, Ya. V. Epstein,* and *L. I. Durinina,* Vysokomolekul. Ssoedin. *3*, No. 4 (1961).

[27] *Ya. V. Epstein, O. P. Golova,* and *L. I. Durinina,* Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1959*, No. 6.

Oligomers and Pleionomers of Synthetic Fiber-Forming Polymers

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The term "oligomer" is defined, and a survey of methods for the isolation and synthesis of cyclic and linear oligoesters, oligourethanes, oligo(acrylonitriles), and oligoamides is presented. The oligomers serve a valuable function as model substances for the investigation of many properties of the corresponding high polymers. This is shown using several examples (infrared spectroscopy, X-ray spectroscopy, viscosity).

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A. Introduction

The work of *Staudinger* [1] on cellulose and other macromolecules led to the realization that many high molecular-weight substances consist of mixtures of molecules which are homologous to the polymer and which differ from each other, often to a considerable degree, in chain length and thus in molecular weight. This heterogeneity in macromolecular substances led *Carothers* [2] to deliberate as early as 1930, that it would be desirable in structural investigations to isolate homogeneous low molecular-weight homologues from polymers. Several years later, *Schlack* [3] was able to detect low molecular-weight linear and cyclic fractions in poly-(ε-caprolactam). Thus he gave the incentive to oligomer research.

Since the last review [4], further advances have been made. Not only have further high molecular-weight members been synthetized in the nylon 6, nylon 6.6, and poly(ethylene terephthalate) series investigated earlier [4], but oligomers have also been prepared from other types of polyamides and from polyurethanes [5–6a], acrylonitrile, and poly-[1,4-bis-(hydroxymethyl)cyclohexane terephthalate], and oligophenylenes [7], oligosiloxanes [8], and oligomers from phenol-formaldehyde condensations [9] have been obtained. In this review, however, only oligomers of fiber-forming polymers are discussed. A few years ago, two comprehensive articles on oligoesters [10, 11] and oligoamides [11] appeared in the Japanese language, as well as another survey of linear and cyclic oligomers [11a].

B. Definitions and Nomenclature

The term "oligomer" was introduced by *van der Want* [12]. We used it in a subsequent review [4] and later *Kern* [12a] defined it more precisely: oligomers are molecularly homogeneous substances of low molecular

[1] *H. Staudinger:* Arbeitserinnerungen. Hüthig-Verlag, Heidelberg 1961.

[2] *W. H. Carothers, J. A. Arvin,* and *G. L. Dorough,* J. Amer. chem. Soc. *52,* 3292 (1930).

[3] *P. Schlack* and *K. Kunz* in *R. Pummerer:* Chemische Textilfasern, Filme u. Folien. Enke-Verlag, Stuttgart 1953, p. 629 et seq.

[4] *H. Zahn* et al., Angew. Chem. *68,* 229 (1956).

[5] See, for example *W. Kern, H. Kalsch, K. J. Rauterkus,* and *H. Sutter,* Makromolekulare Chem. *44–46,* 78 (1961).

[6] *W. Kern, K. J. Rauterkus,* and *W. Weber,* Makromolekulare Chem. *43,* 98 (1961); *W. Kern, K. J. Rauterkus, W. Weber,* and *W. Heitz,* ibid. *57,* 241 (1962).

[6a] *K. J. Rauterkus* and *W. Kern,* Chimia *16,* 114 (1962).

[7] See, for example *W. Kern, W. Gruber,* and *H. O. Wirth,* Makromolekulare Chem. *37,* 198 (1960); *W. Kern, W. Heinz,* and *H. O. Wirth,* ibid. *40,* 189 (1960); 42, 177 (1960).

[8] See, for example *G. Greber* and *L. Metzinger,* Makromolekulare Chem. *39,* 168 (1960).

[9] See, for example *H. Kämmerer,* Angew. Chem. *70,* 390 (1958).

[10] *Shizumobu Hashimoto,* Bull. Inst. chem. Res., Kyoto Univ. *14,* 1036 (1959).

[11] *Ryohei Oda* and *Massaya Okano,* Bull. Inst. chem. Res., Kyoto Univ. *15,* 470 (1960).

[11a] *M. Rothe,* Makromolekulare Chem. *35,* 183 (1960).

[12] *G. M. van der Want* and *A. J. Staverman,* Recueil Trav. chim. Pays-Bas *71,* 379 (1952).

[12a] *W. Kern,* Chemiker-Ztg. *76,* 667 (1962); see also: Makromolekulare Chem. *38,* 1 (1960); *W. Kern* and *R. C. Schulz* in *Houben-Weyl-Müller:* Methoden der organischen Chemie. Thieme, Stuttgart 1961, Vol. 14/1, p. 4; *W. Kern* and *H. Kämmerer* in *R. Houwink* and *A. J. Staverman:* Chemie und Technologie der Kunststoffe. 4th Edit., Akademische Verlagsgesellschaft, Leipzig 1962, Vol. 1, p. 4.

weight, which are homologous with polymers and differ sufficiently in their physical properties to allow their separation into chemically individual compounds. From molecular weights of about 1000 onwards homologues can no longer be separated. In this region, the melting points of the oligomers already closely approach those of the polymer [13]. It can also be shown by infrared spectroscopy and X-ray analysis that the higher oligomers are very similar to the polymers in their properties, and hence can serve as model substances for structural investigations of macromolecular substances. These higher members can no longer be denoted as oligomers [*], *i.e.* entities composed of a few building blocks. It therefore appears desirable to introduce for them the new name "pleionomers" [**]. Pleionomers are therefore molecularly homogeneous substances homologous with the polymers, but no longer sufficiently different from the latter in their physical properties.

Condensation polymers can be synthetized, as is well known, from one kind of monomer (*e.g.*, ε-aminocaproyl-) or from two (*e.g.*, hexamethylenediamine and adipoyl-). Polyamides belonging to the first class always have only amino and carboxyl groups as terminal residues. In the second class, however, three polymer-homologous series can always occur. Thus, in polyamides, these may be compounds containing terminal residues of either one amino and one carboxyl group, or two amino groups, or two carboxyl groups. In polyesters, there may be one hydroxyl and one carboxyl, or two hydroxyls, or two carboxyl groups at the chain ends; in polyurethanes, a similar situation exists with isocyanate residues and OH groups. All the oligomeric condensation products hitherto investigated have also contained cyclic compounds.

In order to facilitate the survey of the various series of homologous oligomers, we introduced abbreviations for the monomer units of nylon 6, nylon 6.6, and poly(ethylene terephthalate) [4]. These are summarized in Table 1, which also includes abbreviations for the basic units of other polyamides, of poly-[1,4-cyclohexylenedimethylene terephthalate] (Kodel®), and of the polyurethane from hexamethylene diisocyanate and 1,4-butanediol (Dorlon®).

Table 1. Abbreviations for the repeating units of oligomers

Compound	Formula	Abbreviation
Caprolactam	$\overline{\text{HN(CH}_2)_5\text{CO}}$	c[Cap]
ε-Aminocaproic acid	$\text{H—HN(CH}_2)_5\text{CO—OH}$	H—[Cap]—OH
ω-Aminoundecanoic acid	$\text{H—HN(CH}_2)_{10}\text{CO—OH}$	H—[Und]—OH
Dodecanolactam	$\overline{\text{HN(CH}_2)_{11}\text{CO}}$	c[Dod]
ω-Aminododecanoic acid	$\text{H—HN(CH}_2)_{11}\text{CO—OH}$	H—[Dod]—OH
Hexamethylenediamine	$\text{H—HN(CH}_2)_6\text{NH—H}$	H—[B]—H
Adipic acid	$\text{HO—OC(CH}_2)_4\text{CO—OH}$	HO—[A]—OH
N-(ω-Aminohexyl)adipamide	$\text{H—HN(CH}_2)_6\text{NH—CO(CH}_2)_4\text{CO—OH}$	H—[B—A]—OH
Sebacic acid	$\text{HO—OC(CH}_2)_8\text{CO—OH}$	HO—[Seb]—OH
N-(ω-Aminohexyl)sebacamide	$\text{H—HN(CH}_2)_6\text{NH—CO(CH}_2)_8\text{CO—OH}$	H—[B—Seb]—OH
Ethylene glycol	$\text{H—O(CH}_2)_2\text{O—H}$	H—[G]—H
Terephthalic acid	HO—OC—C$_6$H$_4$—CO—OH	HO—[T]—OH
Mono-β-hydroxyethyl terephthalate	H—O(CH$_2$)$_2$O—OC—C$_6$H$_4$—CO—OH	H—[G—T]—OH
1,4-Bis(hydroxymethyl)cyclohexane	H—OCH$_2$—C$_6$H$_{10}$—CH$_2$O—H	H—[D]—H
Mono-*p*-(hydroxymethyl)cyclohexylmethyl terephthalate	H—OCH$_2$—C$_6$H$_{10}$—CH$_2$O—OC—C$_6$H$_4$—CO—OH	H—[D—T]—OH
1,4-Butanediol [14]	$\text{HO(CH}_2)_4\text{OH}$	[4]
Hexamethylene diisocyanate [14]	$\text{OCN(CH}_2)_6\text{NCO}$	[h]

It is also seen in Table 1 that the basic units, *e.g.* "B-A" for nylon 6.6, or "Und" for nylon 11, are placed in square brackets. If the basic unit is composed of two monomer units, as in nylon 6.6 or poly(ethylene terephthalate), the hyphen within the brackets denotes an amide or ester bond. The abbreviation for a diamine or diol is always placed at the beginning. To indicate cyclic oligomers, a "c" appears before the brackets. A carbobenzoxy residue, $C_6H_5CH_2OCO-$, used to protect an amino group is denoted by "Z" [15]. We abbreviate the benzyl residue and the thiophenyl group as Bz and SPh, respectively.

C. Preparation of Oligomers

I. Isolation of Oligomers from Technical Polymers

As is well known, low molecular-weight fractions can be extracted from polyamides [3,4,16–22], polyesters [23, 24], and the polyurethane Dorlon® [25,26]. The solvents

[13] *H. Zahn* et al., Angew. Chem. *74*, 599 (1962).

[*] ὀλίγος – few. [**] πλέον – more than a few.

[14] *W. Kern* and *W. Thoma*, Makromolekulare Chem. *11*,10 (1953).

[14a] *W. Kern* and *W. Thoma*, Makromolekulare Chem. *16*, 89, 108 (1955); *W. Kern* and *J. K. Rauterkus*, ibid. *28*, 221 (1958).

[15] *E. Brand*, Ann. New York Acad. Sci. *47*, 187 (1946).

[16] *P. H. Hermans*, Recueil Trav. chim. Pays-Bas *72*, 798 (1953); Nature (London) *177*, 126 (1956).

[17] *D. Heikens*, Recueil Trav. chim. Pays-Bas *75*, 1199 (1956).

[18] *I. Rothe* and *M. Rothe*, Chem. Ber. *88*, 284 (1955); *M. Rothe*, J. Polymer Sci. *30*, 227 (1958).

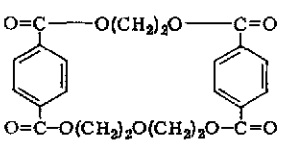
for extraction include water [18,19], methanol [18,19], trichloroethylene [23], dioxan [24], chlorobenzene [25], dimethylformamide [26], and glacial acetic acid [21,22]. The amounts of low molecular-weight material isolated from individual polymers vary considerably (Table 2) and depend further on their pretreatment [20] as well as on the solvent used.

Table 2. Low molecular-weight fractions obtained from some polymers

Polymer	Basic unit	Low molecular-weight fraction [% by wt.]	Solvent for extraction
Nylon 6	—[Cap]—	11—12	Methanol [19]
Nylon 6.6	—[B—A]—	2.0—2.2	Glacial acetic acid [21]
Nylon 6.10	—[B—Seb]—	1	Methanol [27]
Nylon 11	—[Und]—	*ca.* 7	Glacial acetic acid [22]
Dorlon®	—[4—h]—	2.6—3.5	Dimethylformamide[26]
Terylene®	—[G—T]—	1.3—1.7	Dioxan [24]

The low molecular-weight fractions are principally cyclic monomers and oligomers. They may be fractionated by crystallization, selective extraction, or sublimation *in vacuo*. Table 3 summarizes the cyclic oligomers so far isolated on a preparative scale from nylons 6, 11, 6.6, and 6.10, as well as from Terylene®, Kodel®, and Dorlon®. Higher members of the homologous series are always present in the extracts in appreciably lower concentrations than lower members [18,19,24].

The cyclic oligoester c[D-T]$_3$ has an especially wide melting range (Table 3). Presumably, a mixture of *cis* and *trans* isomers is involved. In addition, rearrangements and decompositions during melting are possible. On extraction of Terylene®, in addition to the cyclic oligomers c[G—T]$_n$ (n = 3 to 5), a mixed cyclic bis(terephthalate) of ethylene glycol and 3-oxapentamethylene glycol [*(1)*, m.p. 165—167 °C] has been isolated.

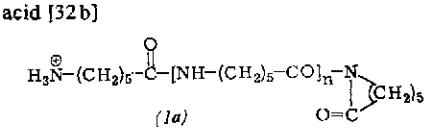


(1)

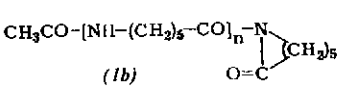
Table 3. Cyclic oligomers isolated from polymers

Compound	M.p. [°C]	Mol. wt. (calcd.)	Ref.
c[Cap]$_2$	348	226.3	[18,28]
c[Cap]$_3$	251	339.5	[18,28]
c[Cap]$_4$	260	452.6	[18,28,29]
c[Cap]$_5$	253	565.8	[29,32]
c[B—A]	253	226.3	[18,20,21]
c[B—A]$_2$	241	452.6	[18,20,21]
c[B—A]$_3$	234—237	678.9	[18c,72,74]
c[B—A]x	266—268	—	[21]
c[B—Seb]	227—228	282.4	[27]
c[Und]$_2$	188	366.6	[22,30]
c[4—h]	164	258.3	[25,26]
c[4—h]$_2$	198	516.6	[26]
c[G—T]$_3$	325—327	576.6	[23,24]
c[G—T]$_4$	225—229	768.8	[24]
c[G—T]$_5$	249—250	961.0	[24]
c[D—T]$_3$	288—298	823.0	[31,31a]

With extracts of nylon 6 and nylon 6.6 it has been possible to detect not only the compounds shown in Table 3, but also, by using chromatography, to identify the homologous cyclic amides c[Cap]$_n$ (n = 6 to 9) [18] and c[B—A]$_n$ (n = 3 or 4) [32], as well as the linear oligomers H—[Cap]$_n$—OH (n = 1 to 4). The proportion of the latter oligomers in the total extract may be less than 0.1 % by weight, however [18]. Recently, polymer-homologous *N*-[oligo-(ε-aminocaproyl)]caprolactams were found in caprolactam polymers, prepared either cationically with anhydrous acids (HCl, H_3PO_4, H_2SO_4) or anionically with alkali metals in the presence of *N*-acetylcaprolactam [32a]. These *N*-[oligo-(ε-aminocaproyl)]caprolactams were present in the form of their ammonium salts *(1a)*, n = 0 to 2, or with an acetyl residue at the terminal amino group *(1b)*, n = 1 to 3. The compounds were detected chromatographically and some were synthetized by condensation of *N*-acyl-ε-aminocaproyl chlorides with caprolactam. In the synthesis of *(1a)*, n = 0, the carbobenzoxy residue was used to protect the amine group; it was afterwards removed with HBr in glacial acetic acid [32b]



(1a)



(1b)

II. Syntheses of Oligomers

1. *Oligomeric Carboxylic Esters*

The synthesis of linear oligoesters from terephthalic acid and ethylene glycol has already been reviewed [4,10]. However, only the lower members of the series of homologous oligomers could be prepared by un-

[19] *H. Spoor* and *H. Zahn*, Z. analyt. Chem. *168*, 190 (1959); *H. Zahn, J. Kunde*, and *G. Heidemann*, Makromolekulare Chem. *43*, 220 (1961).

[20] *C. J. Brown, A. Hill*, and *P. V. Youle*, Nature (London) *177*, 128 (1956).

[21] *H. Zahn, P. Miró*, and *F. Schmidt*, Chem. Ber. *90*, 1411 (1957).

[22] *H. Zahn* and *J. Kunde*, Chem. Ber. *94*, 2470 (1961).

[23] *S. D. Ross, E. R. Coburn, W. A. Leach*, and *W. B. Robinson*, J. Polymer Sci. *13*, 406 (1954).

[24] *I. Goodman* and *B. F. Nesbitt*, Polymer *1*, 384 (1960); J. Polymer Sci. *48*, 423 (1960).

[25] *O. Bayer*, Liebigs Ann. Chem. *549*, 286 (1941); Angew. Chem. *59*, 257 (1947).

[26] *H. Zahn* and *M. Dominik*, Chem. Ber. *94*, 125 (1961).

[27] *G. B. Gleitsmann*, Ph.D. Thesis, Technische Hochschule Aachen, 1962; Makromolekulare Chem. *60*, 45 (1963).

[27a] *H. Zahn* and *G. B. Gleitsmann*, Makromolekulare Chem. *63*, 129 (1963).

[28] *H. Zahn* and *E. Rexroth*, Z. analyt. Chem. *148*, 181 (1955).

[29] *H. Zahn, J. Kunde*, and *G. Heidemann*, Makromolekulare Chem. *43*, 220 (1961).

[30] *P. Miró*, Investigación e Informacion Textil *2*, 13 (1959).

[31] *G. Valk*, Ph.D. Thesis, Technische Hochschule Aachen, 1962.

[31a] *H. Zahn* and *G. Valk*, Polymer Letters *1*, 105 (1963).

[31b] *H. Zahn* and *G. Valk*, Makromolekulare Chem. *64*, 37 (1963).

[32] *M. Rothe*, Chemiker-Ztg. *83*, 230 (1959).

[32a] *M. Rothe, G. Reinisch, W. Jaeger*, and *I. Schopow*, Makromolekulare Chem. *54*, 183 (1962); *M. Rothe* and *I. Rothe*, Angew. Chem. *73*, 769 (1961); Faserforsch. u. Textiltechn. *12*, 448 (1961); *G. Reinisch* and *W. Jaeger*, ibid. *13*, 43, 79 (1962); *K. Gehrke*, ibid. *13*, 95 (1961).

[32b] *D. Ben-Ishai* and *A. Berger*, J. org. Chemistry *17*, 1564 (1952).

equivocal reactions [33,34]. For the synthesis of the higher molecular-weight compounds, the only methods available were oligocondensation and the duplication method [14,35]. Only dibenzyl esters of the homologous oligoesters with two terminal carboxyl groups were accessible by unequivocal reactions [34]. The starting materials here were compounds of the type H–[G–T]$_n$–G–H [33], which had been prepared by an ambiguous method.

In the meantime we have succeeded in finding unequivocal syntheses for the series of homologous oligomers of poly(ethylene terephthalate) [36]. The modern methods of peptide synthesis, whereby oligopeptides can be formed from two monofunctional reactants, served as a model. All other functional groups were blocked by protecting groups. In the synthesis of oligoesters, the benzyl residue serves as the protecting group for both the alcohol and the acid functions (as the benzyl ether and benzyl ester, respectively). It can be removed by hydrogenolysis (H_2/Pd) or with anhydrous aluminum chloride without attack on the other ester bonds [36].

Table 4. Oligoesters from terephthalic acid and ethylene glycol

H–[G–T]$_n$–G–H [33,36]			HO–T–[G–T]$_n$–OH [34,36]		
n	M.p. [°C]	Mol. wt. (calcd.)	n	M.p. [°C]	Mol. wt. (calcd.)
1	109–110	254.2	1	> 360	358.3
2	173–174	446.4	2	280–281	550.5
3	200–205	638.6	3	268–270	742.7
4	213–216	830.8	4	252–255	934.9
5	218–220	1023.0	5	233–236	1127.1
H–[G–T]$_n$–OH [31,33,36]			CH_3O–T–[G–T]$_n$–OCH_3 [31,33]		
n	M.p. [°C]	Mol. wt. (calcd.)	n	M.p. [°C]	Mol. wt. (calcd.)
1	178	210.2	1	168–170	386.3
2	200–205	402.4	2	194–198	578.5
3	219–223	594.6	3	208–212	770.7
			4	219–223	962.9

The synthesis of the important diols, which are key substances for the preparation of oligoesters of the Terylene® type (Table 4), is outlined in equations (a) and (b).

(a) 2 Bz–[G]–H + Cl–[T]–Cl → Bz–[G–T]–G–Bz
$\xrightarrow{H_2(Pd/C)}$ H–[G–T]–G–H

(b) 2 Bz–[G–T]–Cl + H–[G–T]$_n$–G–H → Bz–[G–T]$_{n+2}$–G–Bz
$\xrightarrow{H_2(Pd/C)}$ H–[G–T]$_{n+2}$–G–H

Oligoesters of poly-(1,4-cyclohexylenedimethylene terephthalate) [31,31b] can occur in *cis*- and *trans*-forms as a result of the geometric isomerism of 1,4-bis(hydroxymethyl)cyclohexane. Oligomers of both series have been prepared (Table 5).

Table 5. Oligoesters from terephthalic acid and 1,4-bis(hydroxymethyl)-cyclohexane [31,31b]

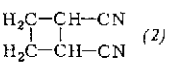
Compound [*]	M.p. [°C]	Mol. wt. (calcd.)
H–[D–T]–OBz (*trans*)	63	382.4
H–[D–T]–OH (*trans*)	175–178	292.3
BzO–T–[D–T]–OBz (*cis*)	107–110	620.7
BzO–T–[D–T]–OBz (*trans*)	170–173	620.7
BzO–T–[D–T]$_2$–OBz (*trans,trans*)	203–206	895.0
HO–T–[D–T]–OH (*cis*)	> 300	440.3
HOT–[D–T]–OH (*trans*)	> 310	440.3
Tos–[D–T]–D–Tos (*trans*)	163–165	726.9

*] Bz = Benzyl; Tos = *p*-Toluenesulfonyl.

No cyclic oligoesters of the Terlyene® or Kodel® types have yet been synthetized; however, synthesis of tetrameric cyclic carbonates of aromatic dihydroxy compounds has recently been achieved [36a].

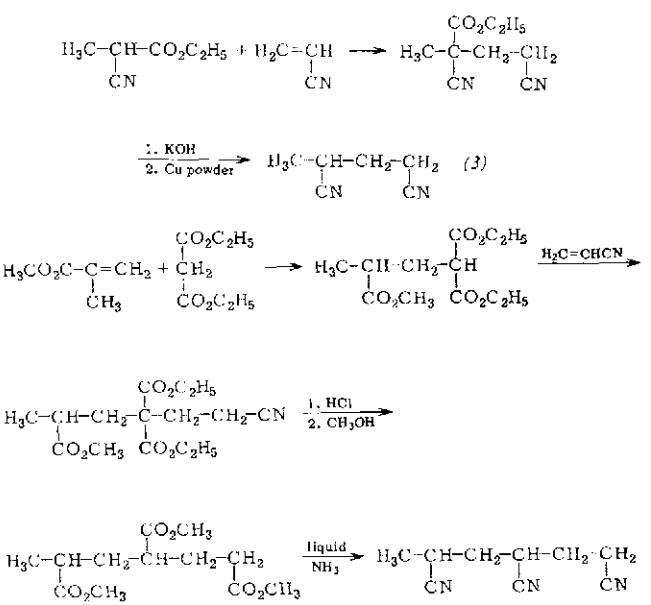
2. *Oligomeric Acrylonitriles*

The oligomers of acrylonitrile are difficult to obtain and only a few have been prepared so far. *Coyner* [37] obtained a cyclic dimer *(2)* from acrylonitrile at 200–300 °C and pressures of 20–130 atm. It was separated by


(2)

fractional distillation into a *cis* and a *trans* isomer. Attempts to obtain linear analogues of acrylonitrile by controlled stepwise polymerization were unsuccessful. No uniform individual compounds were formed; the products consisted mainly of three oligomeric fractions with degrees of polymerization of approximately 6, 7, and 10 and with melting point ranges of 168–175 °C, 175 to 185 °C, and 190–200 °C, respectively [38].

Direct synthesis using cyanoethylation and the Michael addition yielded such individual oligoacrylonitriles as


(3)

(4)

[33] *H. Zahn* and *R. Krzikalla*, Makromolekulare Chem. *23*, 31 (1957).

[34] *H. Zahn* and *B. Seidel*, Makromolekulare Chem. *29*, 70 (1959).

[35] *R. Fordyce, E. L. Lovell*, and *H. Hibbert*, J. Amer. chem. Soc. *61*, 1905 (1939).

[36] *C. Borstlap*, Ph.D. Thesis, Technische Hochschule Aachen, 1960; *H. Zahn, C. Borstlap*, and *G. Valk*, Makromolekulare Chem. *64*, 18 (1963).

[36a] *H. Schnell* and *L. Bottenbruch*, Makromolekulare Chem. *57*, 1 (1962).

[37] *E. C. Coyner* and *W. S. Hillmann*, J. Amer. chem. Soc. *71*, 324 (1949).

[38] *H. Zahn* and *P. Schäfer*, Makromolekulare Chem. *30*, 225 (1959).

1,3-dicyanobutane *(3)*, 1,3,5-tricyanohexane *(4)*, 1,3,5-tricyanopentane *(5)*, and 1,3,5,7-tetracyanoheptane *(6)* [39–40].

1,3-Dicyanobutane *(3)* is also formed by thermal degradation of polyacrylonitrile at 550 °C, together with the monomer and other decomposition products [38]. Japanese authors have recently described the synthesis of 2,4-dicyanopentane and 2,4,6-tricyanoheptane [41]. Both of these compounds, as well as substances *(3)* through *(6)*, are liquid. None of these methods yielded uniform, long-chain oligomers (degree of polymerization of 10 to 12) which would have physical properties approaching those of the polymer.

3. *Oligomeric Urethanes*

Until the development of Spandex® fibers [42,43], the only fiber-forming polyurethane to achieve any industrial importance was the polyadduct Dorlon®, which is made from hexamethylene diisocyanate and 1,4-butanediol. Linear and cyclic oligourethanes of this type (Table 6) have been described several times in recent years [5,6,26,44]. The homologous ω-dihydroxy-oligourethanes *(7)*, n = 1 to 9, have been prepared up to the

Table 6. Oligomers from hexamethylene diisocyanate and 1,4-butanediol

ω-Dihydroxy-oligourethanes [5,44]		
n	M.p. [°C]	Mol. wt. (calcd.)
1	103–105	348.5
2	146	606.6
3	162	865.1
4	169–170	1123.4
5	172–173	1381.7
6	173–174	1640.0
7	175–176	1898.3
9	177–179	2414.9

Cyclo-oligourethanes [6,26]		
n	M.p. [°C]	Mol. wt. (calcd.)
1	164	258.3
2	198	516.6

Bis(chloroformates) [44]		
n	M.p. [°C]	Mol. wt. (calcd.)
1	48	473.4
2	138	731.7
3	162	990.0

Hydrobromides of ω-diamino-oligourethanes [44]		
n	M.p. [°C]	Mol. wt. (calcd.)
1	228	536.4
2	226	794.7
3	218	1053.0
4	212	1311.4

nonamer [5] by means of the duplication method (n = 1, 3, 7) [14,14a], or by stepwise synthesis with bifunctional reactants [5]. For example, in order to prepare

$$HO(CH_2)_4O-[CO-NH(CH_2)_6NH-CO-O(CH_2)_4O]_n-H \quad (7)$$

the monomeric diol by the duplication method, hexamethylene diisocyanate is treated with a 200-fold excess of 1,4-butanediol.

[4] (excess) + [h] → [4] ! [4-h-4] (1st duplication)

Using the same scheme, the trimer (2nd duplication) and the heptamer (3rd duplication) can be prepared, except that the diol component in these cases is, respectively, the monomeric or the trimeric ω-dihydroxy oligourethane. In the second and third duplication, it is no longer possible to remove the excess diol by distillation. It can be removed only by extraction. Thus, the excess of diol must be reduced, and this expedient in turn leads to formation of as much as 20 % of higher molecular-weight products. Because of their similar solubilities, these cannot be completely separated from the main product even by repeated fractionation; hence the products, although sharply defined fractions, are not individual compounds. The remaining ω-dihydroxy oligourethanes can be obtained by a two-step reaction [equations (c) and (d)].

(c) [4] + [h] (excess) → [h] + [h-4-h] + $[h\text{-}4]_n$–h

(d) [h-4-h] + [4] (excess) → [4] + $[4\text{-}h]_2$-4 + $[4\text{-}h]_n$–4

However, application of this synthetic principle to the preparation of higher members of the ω-dihydroxy oligourethane series leads to the same problems as the pure duplication method; here, too, one obtains only relatively sharp fractions instead of pure compounds.

Oligomers with isocyanate end groups (diisocyanates or hydroxyisocyanates) are difficult to obtain in pure form because of the reactivity of the isocyanate group.

Hydrobromides of homologous ω-diamino-oligourethanes (terminated by hexamethylenediamine), which contain the basic structure of the diisocyanates, have been prepared up to the tetramer [44]. Thus, for example, 1,4-butanediol or ω-dihydroxy-oligourethanes (n = 1 to 3) are treated with phosgene to form the bis(chloroformates) *(8)*, which are treated with monocarbobenzoxyhexamethylenediamine [45] to yield the bis(benzyl)urethanes *(9)*. On cleavage of the carbobenzoxy residue with HBr in glacial acetic acid [46], the ω-diamino-oligourethanes are obtained as their hydrobromides *(10)*.

$$Cl-\overset{O}{\overset{\|}{C}}-O(CH_2)_4O-[CO-NH(CH_2)_6NH-CO-O(CH_2)_4O]_n-COCl$$

$$\downarrow (8)$$

$$H_5C_6-CH_2O-[CO-NH(CH_2)_6NH-CO-O(CH_2)_4O]_n-CO-NH(CH_2)_6NH-\overset{O}{\overset{\|}{C}}-OCH_2-C_6H_5$$

$$\downarrow (9)$$

$$HBr\cdot H-[NH(CH_2)_6NH-CO-O(CH_2)_4O-CO]_n-NH(CH_2)_6NH_2\cdot HBr \quad (10)$$

Beside the linear oligomers of the Dorlon® type indicated in Table 6, the cyclic oligourethanes c[4-h] and c$[4\text{-}h]_2$, isolated from the polyadduct, have also been synthetized. The synthesis was effected by reaction of hexamethylenediamine with the bis(chloroformates) of 1,4-butanediol or of monomeric ω-dihydroxy-oligourethane, respectively. Compounds of the type c[4-h] can also be obtained in very dilute solution from hexamethylene diisocyanate and 1,4-butanediol [6].

4. *Oligomeric Carboxamides*

a) Linear Oligoamides

These compounds may be prepared by partial hydrolysis of the polymers [4], by oligocondensation [4,48],

[39] *H. Zahn* and *P. Schäfer*, Chem. Ber. *92*, 736 (1959).

[40] *R. C. Houtz*, Textile Res. J. *20*, 786 (1950).

[41] *T. Takata, H. Ishii, J. Nishiyama*, and *M. Taniyama*, Chem. High Polymers (Tokyo) *18*, No. 192, 235 (1961).

[42] Chem. Engng. News *40*, No. 5, 34 (1962).

[43] *H. Rinke*, Chimia *16*, 93 (1962); Angew. Chem. *74*, 612 (1962); Angew. Chem. internat. Edit. *1*, 419 (1962).

[44] *H. Zahn* and *M. Dominik*, Makromolekulare Chem. *44–46*, 290 (1961).

[45] *H. Zahn* and *F. Schmidt*, Makromolekulare Chem. *36*, 1 (1959).

[46] *D. Ben-Ishai* and *A. Berger*, J. org. Chemistry *17*, 1564 (1952).

[47] *H. Stetter* and *J. Marx*, Liebigs Ann. Chem. *607*, 59 (1957).

[48] *H. Zahn* and *W. Lauer*, Makromolekulare Chem. *23*, 85 (1957).

or by means of the duplication method [48].The degree of purity of the products so obtained is unsatisfactory, however, since by-products are also formed which cannot be separated off completely because of their similar solubilities.

Homogeneous individual oligomers may be synthetized according to the methods of peptide chemistry via the reaction of monofunctional components. The acid chloride method [4,12,49,49a] of *Emil Fischer* has been used to generate the amide bond. Oligoamides can also be synthetized by ester aminolysis [4,49]. However, this method is suitable only for the preparation of the initial members of the three linear oligomer-homologous series of nylon 6.6 and nylon 6.10, especially for the monomeric amino acids H-[B-A]-OH [45] and H-[B-Seb]-OH [27], which are important starting compounds. The anhydride method [50] is the one most frequently used. It has been employed for the synthesis of homologous linear oligoamides of nylon 6 [51–53a], nylon 11 [54], nylon 6.6 [45,56–58], and nylon 6.10 [27], and oligomeric copolymers of ε-aminocaproic acid with ω-aminoundecanoic acid (nylon 6.11) [59]; see Tables 7 through 12. Equation (e) illustrates the synthesis of oligomers of ω-amino acids, using oligo-ε-aminocaproic acid [51] as an example.

Table 7. Oligomers of nylon 6

Oligomeric amino acids [12,49a,51,70] $H-[Cap]_n-OH$			Cyclic oligoamides [4,28,66,67,70] $c[Cap]_n$			Oligoamides with protected end groups [53] $C_2H_5CO-[Cap]_n-NHC_3H_7$		
n	M.p. [°C]	Mol. wt. (calcd.)	n	M.p. [°C]	Mol. wt. (calcd.)	n	M.p. [°C]	Mol. wt. (calcd.)
1	202–203	131.2	1	69.5	113.2	1	106	228.3
2	197–198	244.3	2	348	226.3	2	149	341.5
3	203–204	357.5	3	247	339.5	3	172	454.7
4	206–207	470.7	4	261	452.6	4	181	567.8
5	207–208	583.8	5	253	565.8	5	187	681.0
6	209–210	697.0	6	260	679.0	6	191	794.2
7	209–210	810.1	7	236	792.1	7	197	907.3
8	210–211	923.3	8	226–230	905.3	8	200	1020.5
9	208–211	1036.5	9	224–226	1018.4	9	201	1133.6
10	212–213	1149.6				10	201	1246.8
11	209–212	1262.8				11	204	1360.0
12	211–213	1375.9				12	202	1473.1
						13	200	1586.3
						14	205	1699.3
						15	206	1812.6
						16	206	1925.8

Table 8. Oligomers of nylon 6.6

$H-[B-A]_n-OH$ [4,45,48,57,72]			$HCl\cdot H-[B-A]_n-B-H\cdot HCl$ [56]			$HO-A-[B-A]_n-OH$ [4,48,56,57]		
n	M.p. [°C]	Mol. wt. (calcd.)	n	M.p. [°C]	Mol. wt. (calcd.)	n	M.p. [°C]	Mol. wt. (calcd.)
1	190	244.3	1	248–250	415.4	1	188–189	372.4
2	222	470.6	2	249–251	641.7	2	200–205	598.7
3	246–248	696.9	3	254–255	868.0	3	210–211	825.0
4	246–248	923.2	4	–	1094.3	4	214–219	1051.3
5	247–252	1149.5	5	236–240	1320.6			
$c[B-A]_n$ [4,57,68,72,74]			$C_2H_5CO-[B-A]_n-B-COC_2H_5$ [58]			$C_3H_7NH-A-[B-A]_n-NHC_3H_7$ [58]		
n	M.p. [°C]	Mol. wt. (calcd.)	n	M.p. [°C]	Mol. wt. (calcd.)	n	M.p. [°C]	Mol. wt. (calcd.)
1	253	226.3	1	202–203	454.7	1	229–230	454.7
2	241	452.6	2	226–228	681.0	2	239–242	681.0
3	233–235	678.9	3	229–231	907.3	3	248–250	907.3
4	236–239	905.2				4	257–260	1133.6
						5	258–261	1359.9

[49] *C. D. Cowell*, Chem. and Ind. *1954*, 577.

[49a] *G. M. van der Want, H. Peters*, and *P. Inklaar*, Recueil Trav. chim. Pays-Bas *71*, 1221 (1952).

[50] *R. A. Boissonas*, Helv. chim. Acta *34*, 874 (1951); *Th. Wieland* and *H. Bernhard*, Liebigs Ann. Chem. *572*, 190 (1951); *J. R. Vaughan* and *R. L. Osato*, J. Amer. chem. Soc. *74*, 676 (1952).

[51] *H. Zahn* and *D. Hildebrand*, Chem. Ber. *90*, 320 (1957); *92* 1963 (1959).

[52] *D. Hildebrand*, Ph.D.Thesis, Universität Heidelberg, 1957.

[53] *B. Dallmann*, Ph.D.Thesis, Technische Hochschule Aachen, 1961.

[53a] *M. Rothe* and *F. W. Kunitz*, Liebigs Ann. Chem. *609*, 88 (1957).

[54] *H. Zahn, H. Roedel* and *J. Kunde*, J. Polymer Sci. *36*, 539 (1959).

[55] *H. Stolper*, Diploma Thesis, Universität Erlangen, 1962.

[56] *J. Shah*, Ph.D.Thesis, Technische Hochschule Aachen, 1960.

[57] *P. Kusch*, Diploma Thesis, Technische Hochschule Aachen, 1960.

[58] *O. P. Garg*, Ph.D.Thesis, Technische Hochschule Aachen, 1963.

[59] *H. Zahn* and *W. Pieper*, Makromolekulare Chem. *53*, 103 (1962).

Table 9. Oligomers of Nylon 6.10

H–[B–Seb]$_n$–OH [27]			H–[B–Seb]$_n$–B–H [27,49]		
n	M.p. [°C]	Mol. wt. (calcd.)	n	M.p. [°C]	Mol. wt. (calcd.)
1	187–188	300.4	1	129–131	398.6
2	198–201	582.8	2	177–179	681.1
3	201–205	865.3	3	203–210	963.5
HO–Seb–[B–Seb]$_n$–OH [27,49]			c[B–Seb]$_n$ [27,47]		
n	M.p. [°C]	Mol. wt. (calcd.)	n	M.p. [°C]	Mol. wt. (calcd.)
1	156–159	484.6	1	227–228	282.4
2	182–184	767.1	1	223–225	564.8

Table 10. Oligomers of nylon 11

H–[Und]$_n$–OH [54,63]			c[Und]$_n$ [22,75]		
n	M.p. [°C]	Mol. wt. (calcd.)	n	M.p. [°C]	Mol. wt. (calcd.)
1	176	201.3	1	155	183.3
2	176–177	384.6	2	186	366.6
3	177–178	567.9	3	183–184	549.9
4	177–179	751.2			
5	(169–171)	934.5			

Table 11. Oligomers of nylon 12 [55]

H–[Dod]$_n$–OH			c[Dod]$_n$		
n	M.p. [°C]	Mol. wt. (calcd.)	n	M.p. [°C]	Mol. wt. (calcd.)
1	184	215.3	1	155	197.3
2	192–193	412.6	2	201–202	394.6
3	(175–177)	608.9	3	175	531.9

Table 12. Nylon 6.11 oligomers [52, 59, 69]

	M.p. [°C]	Mol. wt. (calcd.)		M.p. [°C]	Mol. wt. (calcd.)
H–[Cap–Und]–OH	190–192	314.4	c[Cap–Und]	187–189	296.4
H–[Cap–Und]$_2$–OH	193–194	620.9	c[Cap$_2$–Und]	181	409.5
H–[Cap–Und–Cap]–OH	205	427.6	c[Cap$_3$–Und]	191	522.7
H–[Und–Cap]–OH	178	314.4	c[Cap–Und$_2$]	193–195	479.7
H–[Und–Cap$_2$]–OH	182–184	427.6			
H–[Cap$_2$–Und]–OH	186–187	427.6			
H–[Cap$_3$–Und]–OH	148	540.7			

(e) $Z\text{–[Cap]}_n\text{–OH} \xrightarrow{ClCO_2C_2H_5,\ N(C_2H_5)_3} Z\text{–[Cap]}_n\text{–OCO}_2C_2H_5 \xrightarrow{H\text{–[Cap]}_m\text{–ONa}}$

$Z\text{–[Cap]}_{n+m}\text{–ONa} \xrightarrow[2.\ H_2/Pd]{1.\ HCl} H\text{–[Cap]}_{n+m}\text{–OH}$

Oligomers made from dicarboxylic acids and diamines (nylons 6.6 and 6.10) are prepared by a basically similar method. Oligomers of the type H–[B–A]$_n$–OH and H–[B–Seb]$_n$–OH ($n > 1$) are synthetized according to the same scheme as oligomers of ω-amino acids. Hydrogenolysis to remove the protective group presents some difficulty with the sparingly soluble higher members. Here, the carbobenzoxy group can be detached by means of concentrated hydrochloric acid at 40 °C [60].

[60] *R. B. Merrifield* and *D. W. Woolley*, J. Amer. chem. Soc. *78*, 4646 (1956).

Oligomeric carboxamides having two terminal carboxyl groups are obtained according to equations (f) to (h).

(f) $2\ H_5C_2O\text{–[A]–OH} \xrightarrow[2.\ H\text{–[B]–H}]{1.\ ClCO_2C_2H_5} H_5C_2O\text{–A–[B–A]–OC}_2H_5$

$\xrightarrow[2.\ HCl]{1.\ KOH} HO\text{–A–[B–A]–OH}$

(g) $HO\text{–[A]–OH} \xrightarrow[2.\ 2\ H\text{–[B–A]}_n\text{–OH}]{1.\ 2\ ClCO_2C_2H_5} HO\text{–A–[B–A]}_{2n}\text{–OH}$

(h) $HO\text{–A–[B–A]–OH} \xrightarrow[2.\ 2\ H\text{–[B–A]}_n\text{–OH}]{1.\ 2\ ClCO_2C_2H_5} HO\text{–A–[B–A]}_{2n+1}\text{–OH}$

Oligomers having two terminal amino groups, H–[B–A]$_n$–B–H and H–[B–Seb]$_n$–B–H, are prepared via their bis(carbobenzoxy) derivatives. The protecting group can be removed from the lower members of the series with H_2/Pd; with the higher members, concentrated hydrochloric acid must be used.

End groups can interfere in physicochemical studies. It is then necessary to block them with aliphatic residues which, for their part, will not objectionably interfere with the properties of the oligomers. Protection of the amino group is suitably accomplished with propionyl residues, while the carboxy group is blocked with n-propylamine. Syntheses of oligomers with end groups protected in this way have been carried out according to equation (i) for the nylon 6 [53] and nylon 6.6 [58] types. The amide linkages were formed by means of the anhydride method.

(i) $H_5C_2CO\text{–[Cap]}_n\text{–OH} \xrightarrow[2.\ H\text{–[Cap]}_m\text{–NHC}_3H_7]{1.\ ClCO_2C_2H_5} H_5C_2CO\text{–[Cap]}_{n+m}\text{–NHC}_3H_7$

A few lower members of the homologous series C_2H_5CO–[Cap]$_n$–OH were prepared by the azide method.

$H_5C_2CO\text{–[Cap]–OC}_2H_5 \xrightarrow{N_2H_4} H_5C_2CO\text{–[Cap]–NH–NH}_2$

$\xrightarrow{HCl/NaNO_2} H_5C_2CO\text{–[Cap]–N}_3 \xrightarrow[2.\ H^{\oplus}]{1.\ H\text{–[Cap]}_n\text{–ONa}}$

$H_5C_2CO\text{–[Cap]}_{n+1}\text{–OH}$ (n = 1 to 4)

The solubility of oligomers decreases as the chain length increases. Hence the coupling of long-chain blocks to form higher oligoamides according to the foregoing methods leads to difficulties. It is more advantageous in these cases to use *N,N'*-dicyclohexylcarbodiimide [61]

[61] *J. C. Sheehan* and *G. P. Hess*, J. Amer. chem. Soc. 77, 1067 (1955).

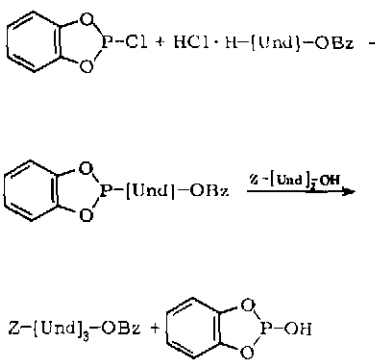
(DCC) or *o*-phenylenephosphoryl monochloride [62] in boiling solvents. Thus, using the carbodiimide method [61], linear oligoamides of nylon 11 *(11)* [54,63] have been synthetized, as well as oligomers of nylon 6

$$Z\text{–}[Und]_2\text{–}OH + DCC + HCl\cdot H\text{–}[Und]_2\text{–}OBz \xrightarrow{N(C_2H_5)_3} Z\text{–}[Und]_4\text{–}OBz$$

(11)

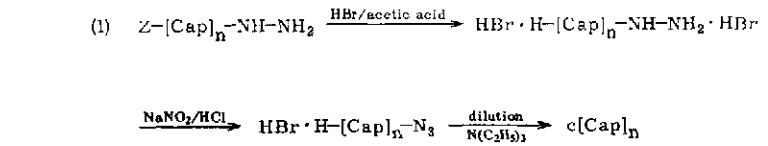
(n + m = 13 to 16) with alkylated end-groups. This method is particularly simple from the preparative point of view, since the building blocks need not be first converted into active derivatives.

Formation of linkages by the phosphitamide method [64] is somewhat more involved; here the amino group must be activated. This method has been applied for the synthesis of oligoamides of nylon 11 [Equation (k)].

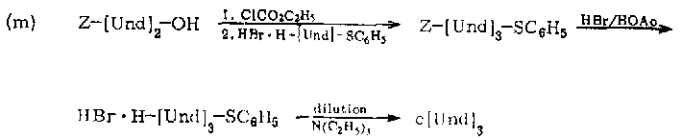
(k) 

b) Cyclic Oligoamides

Cyclic oligoamides can also be obtained by various routes. In most cases the ring is formed by intramolecular reaction of the chain ends in dilute solutions. Cyclization using the azide method [65] requires low temperatures. The following cycloamides have been prepared in this way [equation (l)]: c[Cap]$_n$ (n = 2 to 9) [66,67]; c[B–A]$_n$ (n = 1 and 2) [68]; c[Und]$_2$ [22]; c[Dod]$_2$ [55]; and c[Cap$_m$–Und$_n$] (m = 1 to 3, n = 1; m = 1, n = 2) [69].

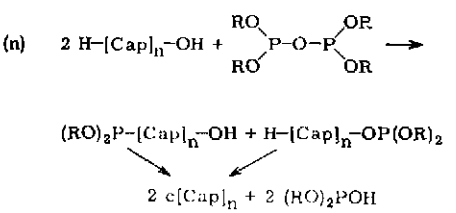
(l) 

The thiophenyl ester method [70] [equation (m)] permits the use of higher temperatures (up to 150 °C). It is therefore particularly suitable for the cyclization of long-chain oligoamides, where the azide method is not applicable because of the low solubility of the reactants.

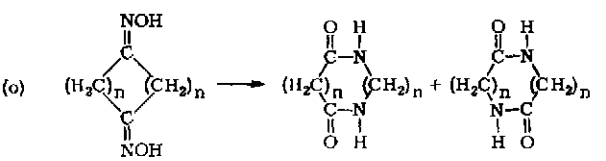
(m) 

In addition to the cyclic oligoamide c[Und]$_3$, syntheses according to equation (m) have been accomplished for the cyclic amides c[Cap]$_n$ (n = 2 to 6) [70], c[B–A]$_n$ (n = 1 to 4) [57, 71], and c[B–Seb]$_2$ [27]. Instead of the thiophenyl ester, it is also possible to use the *p*-nitrophenyl ester [70,72] or the 2,4-dinitrophenyl ester [70].

By activating the amino group with tetraethyl pyrophosphite [73] or other derivatives of phosphorous acid, *Rothe* [74] prepared the cyclic amides c[Cap]$_n$ (n = 2 and 3) and c[B–A]$_n$ (n = 1 to 3) according to equation (n). This method has the advantage that it permits one-step transformation of the unsubstituted linear oligomers into cyclic oligomers.

(n) 

The cyclic oligoamides c[B–A] and c[B–Seb] may also be obtained in high yield from hexamethylenediamine and adipoyl or sebacoyl chlorides [47]. Higher homologues, however, cannot be synthetized in this way. Cyclic diamides can be obtained without resorting to the dilution principle by using

(o) 

Schmidt or Beckmann rearrangements of symmetrical cyclic diketones or oximes, respectively, to effect ring enlargement [75] [equation (o)]. Separation of the mixture of isomers into its components becomes more difficult with increasing ring size; hence, the pure cyclic diamide c[Und]$_2$ could not be obtained by this method.

c) Derivatives of Oligoamides

α) Reduction of Oligoamides with Lithium Aluminum Hydride

Carboxyl groups are reduced to CH_2OH groups by means of $LiAlH_4$. Thus, this reagent permits the con-

[62] *R. Anschütz*, Ber. dtsch. chem. Ges. *76*, 222 (1943).

[63] *H. Roedel*, Ph.D.Thesis, Technische Hochschule Aachen, 1958.

[64] *G. W. Anderson* and *R. W. Young*, J. Amer. chem. Soc. *73*, 501 (1951); *74*, 5307 (1952).

[65] *J. C. Sheehan* and *W. L. Richardson*, J. Amer. chem. Soc. *76*, 6329 (1954); *77*, 6391 (1955).

[66] *H. Zahn* and *H. Determann*, Chem. Ber. *90*, 2176 (1957).

[67] *H. Zahn* und *J. Kunde*, Angew. Chem. *69*, 713 (1957); *70*, 189 (1958).

[68] *H. Zahn* and *F. Schmidt*, Chem. Ber. *92*, 1381 (1959).

[69] *H. Zahn* and *W. Pieper*, Chem. Ber. *95*, 1069 (1962).

[70] *M. Rothe* and *F. W. Kunitz*, Liebigs Ann. Chem. *609*, 88 (1957).

[71] *H. Zahn* et al. in *W. Kern:* Symposium über Makromoleküle, Wiesbaden 1959, Short communications. Verlag Chemie, Weinheim/Bergstr. 1959, Section IV A9.

[72] *P. Kusch*, Ph.D.Thesis, Technische Hochschule Aachen, 1963.

[73] *G. W. Anderson, J. Blodinger*, and *A. D. Welcher*, J. Amer. chem. Soc. *74*, 5309 (1952).

[74] *M. Rothe, I. Rothe, H. Brünig*, and *K. D. Schwenke*, Angew. Chem. *71*, 700 (1959).

[75] *M. Rothe*, Chem. Ber. *95*, 783 (1962).

version of linear and cyclic oligoamides into oligoamines. For example, on reduction of caprolactam-free hot water extracts of nylon 6, it was possible to isolate the cyclic amines $c[NH(CH_2)_6]_n$ (n = 1 to 6). Fractional sublimation *in vacuo* was sufficient to effect separation of the oligomers up to the tetramers; the higher homologues (n = 5 or 6) were obtained by countercurrent distribution [76]. The dimer and tetramer were also synthetized by reduction of the cyclic amides from hexamethylenediamine and adipic acid [21,47,77]. The cyclic amines $c[NH(CH_2)_6NH(CH_2)_{10}]_n$ (n = 1 [27,47]; 2 [27]) were obtained similarly from the cyclic oligoamides of nylon 6.10.

Reduction of the oligo-(ε-aminocaproic acids) $H-[Cap]_n-OH$ leads to the amino alcohols $H-[NH(CH_2)_6]_n-OH$ (n = 1 to 9) [78]. By starting from the corresponding carbobenzoxy derivatives, the methylation products $CH_3-[NH(CH_2)_6]_n-OH$ (n = 1 to 9) are obtained [78]. In the same way, linear oligoamides of nylon 6,10 are converted into the corresponding amino alcohols $H-[NH(CH_2)_6NH(CH_2)_{10}]_n-OH$ (n = 1 to 3), the basic diols $HO(CH_2)_{10}-[NH(CH_2)_6NH(CH_2)_{10}]_n-OH$ (n = 1 to 3), and the diamines $H-[NH(CH_2)_6NH(CH_2)_{10}]_n-NH(CH_2)_6NH_2$ (n = 1 to 3) [27a].

Both the linear and the cyclic amines contain tightly bound water of crystallization, which cannot be removed by drying *in vacuo* at room temperature. The hydrates of the cyclic oligoamines are presumably molecular inclusion compounds, which are stabilized by hydrogen bridges [76]. The water of crystallization contained in the open-chain amines amounts to approximately 0.5 mole per secondary amine group [78].

β) Dinitrophenyl Derivatives of Oligoamides

The primary amine groups of oligoamides react with 1-fluoro-2,4-dinitrobenzene to give the corresponding *N*-dinitrophenyl compounds [79]. Table 13 summarizes

Table 13. Dinitrophenyl (DNP) compounds of linear oligoamides

$DNP-[B-A]_n-B-DNP$		$DNP-[B-A]_n-OH$	
n	M.p. [°C]	n	M.p. [°C]
1	115–117	1	122–124
2	168–171	2	134–141
3	206–209	3	186–188
4	217–222		
5	226–230		

the *N*-dinitrophenyl derivatives of nylon 6.6 oligomers [56]. It is possible to determine the amino nitrogen content of an oligoamide colorimetrically by means of these intensely yellow compounds [56].

D. Properties of Oligomers

I. Analysis

Elemental analysis is often insufficient for the identification of linear oligomers, since the analytical values obtained vary only slightly, especially for the higher homologues. End-group determinations (amino nitrogen by the methods of *van Slyke* [80] or *Sanger* [79], titration [80a]) is the more valuable and preferred approach particularly with the oligoamides. The ω-dihydroxy-oligourethanes may be identified by preparation of the corresponding dichloro- or dibromophenyl derivatives [5]. Oligoesters can be identified by means of their saponification number [33].

The ring size of cyclic oligomers was successfully established in many cases by cryoscopic molecular-weight determinations in camphor or hexahydro-*p*-aminobenzoic acid lactam [18,21]. Better results are obtained with a thermoelectric vapor-pressure osmometer, which can be used to determine the molecular weights of both linear and cyclic oligomers. Suitable solvents are dioxan for the oligoesters [31] and trifluoroethanol for the oligoamides [72].

The purity of oligoamides can be tested qualitatively by paper chromatography. Useful solvent mixtures are 2-butanol/formic acid/water [4], 2-butanol/ammonia/water [4], or tetrahydrofuran/petroleum ether/water [18]. The last system is especially suitable for the separation of cyclic oligoamides of nylons 6 and 6.6, which can also be separated (after reduction to the cyclic amines) by using 2-butanol/formic acid/water [19,76].

II. Melting Points

As the chain length increases, the melting points of the linear oligoamides, oligoesters, and oligourethanes increase and approach the melting point of the high polymer [13].

Oligomers with two terminal carboxyl groups $HO-T-[G-T]_n-OH$ constitute an exception. The first member melts higher than the polymer; however, even in this case the melting point approaches that of Terylene® as the chain length increases.

The amines obtained by reduction of the linear oligoamides of nylons 6 and 6.10 melt between 50 and 90 °C, and here again the melting point rises with chain length. The melting points of the cyclic oligomers alternate within a homologous series (Fig. 1).

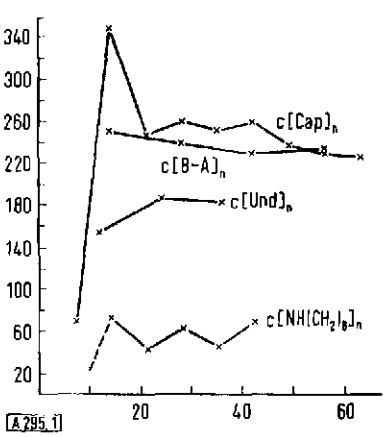


Fig. 1. Melting points of cyclic oligomers of nylon 6, nylon 11, nylon 6.6, and the cyclic amines $c[NH(CH_2)_6]_n$.
Ordinate: Melting point [°C]
Abscissa: Number of ring atoms (n)

[76] *H. Zahn* and *H. Spoor*, Chem. Ber. *89*, 1296 (1956); *92*, 1375 (1959); Angew. Chem. *68*, 616 (1956).
[77] *M. A. Th. Rogers*, Nature (London) *177*, 128 (1956).
[78] *H. Zahn* and *A. Gleissner*, J. Polymer Sci. *54*, 101 (1961).
[79] *F. Sanger*, Biochem. J. *39*, 507 (1945).
[80] *D. D. Van Slyke*, J. biol. Chemistry *9*, 195 (1911); *23*, 407 (1915).
[80a] *W. Pätzold*, Polymer Letters *1*, 269 (1963).

Alternation of melting points is also observed in other cyclic homologues. According to *Dale* [81], the melting point of a ring compound is determined by the stability of its conformation. A strain-free, and hence stable, conformation is usually attained only by compounds having an even number of atoms on the ring. Consequently, these have higher melting points and lower entropies of melting then their neighboring homologues with odd numbers of ring atoms. For example, the compound c[Cap]$_2$ has a diametric arrangement of its amide bonds. This good spatial arrangement leads to a high stability, and hence, to a high melting point. On the other hand, a strain-free conformation is impossible in the monomeric cyclic amide of nylon 6.6.

III. Viscosity

In oligoesters [36,101], oligourethanes [44], and oligoamides [56], the viscosity is a function of molecular weight. The relationships $[\eta] = K \cdot M^a$ [36,101] or $[\eta] = K \cdot M + C$ [44,56] apply here; both of these are derived from the Staudinger viscosity law [102] $[\eta] = K \cdot M$. Deviations occur only among the initial members of the homologous series.

IV. Water-Absorbing Capacity

The ability of oligomers to absorb water leads to certain conclusions regarding their degree of crystallinity, since only the amorphous regions can take up measurable quantities of moisture [103]. Completely crystalline substances should adsorb little or no water vapor. The fact that the absorption of water in oligoamides of nylon 6.6 [56] and of nylon 6.10 [27] depends on the relative humidity of the air denotes the incomplete crystallinity of these compounds. The adsorption centers in the oligoamides are the amino, carboxy, and carboxamide groups [104].

The determination of absorption and desorption curves for the oligoamides of nylon 6.6 [56] yields hysteresis loops such as are also found in polyamide fibers.

If the water uptake of oligoamides of nylon 6.10 is measured at constant conditions, *e.g.* 65 % relative humidity and 21 °C, it is found that the moisture uptake per monomer unit within a homologous series increases with chain length more strongly than would be expected from the increasing number of carboxamide groups. This shows that the crystallinity decreases in the same direction [27].

V. Dyeing Experiments

The dyeing properties of synthetic fibers are of considerable importance with regard to their application. The oligomers can be of value as molecularly homogeneous model substances for the elucidation of dyeing processes. Thus treatment of oligomers of nylon 6 [51,105] and of nylon 6.6 [56] with Crystal Ponceau 6R at pH 2 led to analytically pure dye salts. The acidic dibasic dye reacts bifunctionally with the free amino end-groups of the oligomers, hence the dye uptake becomes smaller with increasing chain length. Oligoamides which contain no free amino groups are not dyeable at pH 2. The dye reacts with the carboxamide groups only at pH 1; these dyeings, however, are very weak and can be washed out with water.

An attempt to achieve fast dyeings of the oligoesters BzO–T–[G–T]$_3$–OBz and H–[G–T]$_3$–G–H with dispersion dyes met with failure. Dispersion dyes are probably fixed by polyester fibers only in the amorphous regions. Hence the above oligoesters must possess high crystallinity.

VI. Ultraviolet and Infrared Spectra

Studies of oligoesters [36,82] and a few oligourethanes [44] reveal that the characteristic ultraviolet absorption bands of the high polymer appear even in the low molecular-weight compounds. In the linear oligomers, in addition to the infrared absorption bands of the high polymer, there are also bands characteristic of the end groups. In a given homologous series, their intensity decreases with increasing chain length. The first members of any homologous series of cyclic oligomers still retain individual infrared spectra, and are therefore suitable as models for spectroscopic conformational analysis [87]. Because of the absence of end groups, the higher cyclic oligomers are especially useful as model substances for the elucidation of the spectrum of the polymer. The infrared spectrum of poly(ethylene tere-

[81] *J. Dale*, J. chem. Soc. (London) *1963*, 93; *J. Dale* and *R. Coulon*, ibid., in the press.

[82] *B. Seidel*, Z. Elektrochem. Ber. Bunsenges. physik. Chem. *62*, 214 (1958).

[83] *R. G. J. Miller* and *H. A. Willis*, Trans. Faraday Soc. *49*, 433 (1953).

[84] *I. M. Ward*, Chem. and Ind. *1956*, 905.

[85] *S. Krimm*, Fortschr. Hochpolymeren-Forsch. *2*, 51 (1960).

[86] *C. G. Cannon*, Spektrochim. Acta *16*, 302 (1960).

[87] *G. Heidemann* and *H. Zahn*, Makromolekulare Chem. *62*, 123 (1963).

[88] *A. Colthup*, J. opt. Soc. America *40*, 397 (1950).

[89] *H. v. Dietrich*, *H. Zahn*, and *H. Spoor*, Z. Naturforsch. *12b*, 665 (1957).

[90] *H. v. Dietrich*, *H. Zahn*, and *F. Schmidt*, Acta crystallogr. *10*, 477 (1957).

[91] *H. v. Dietrich*, *H. Zahn*, and *H. Spoor*, Acta crystallogr. *10*, 468 (1957).

[92] *W. L. Haas*, Acta crystallogr. *14*, 895 (1961).

[93] *H. Zahn* in *W. Kern:* Symposium über Makromoleküle, Wiesbaden 1959, Short communications. Verlag Chemie, Weinheim/Bergstr. 1959, Section 1 B 8.

[94] *L. Sandeman* and *A. Keller*, J. Polymer Sci. *19*, 401 (1956).

[95] *W. Kern*, *J. Davidovits*, *K. J. Rauterkus*, and *G. F. Schmidt*, Makromolekulare Chem. *43*, 106 (1961).

[96] *K. Heß* and *H. Kießig*, Naturwissenschaften *31*, 171 (1943); Z. physik. Chem. *193*, 196 (1944).

[97] *H. Zahn* and *H. Kohler*, Kolloid-Z. *118*, 115 (1950); *H. Zahn* and *U. Winter*, ibid. *128*, 142 (1952).

[98] *H. Zahn* and *W. Pieper*, Kolloid-Z. *180*, 97 (1962).

[99] *A. Keller*, Phil. Mag. *2*, 1171 (1957); Makromolekulare Chem. *34*, 1 (1959); J. Polymer Sci. *36*, 361 (1959); *A. Keller* and *A. O'Connor*, Polymer *1*, 163 (1960).

[100] *E. W. Fischer*, Z. Naturforsch. *12a*, 753 (1957); Angew. Chem. *74*, 551 (1962); Angew. Chem. internat. Edit. *1*, 488 (1962); *R. Eppe*, *E. W. Fischer*, and *H. A. Stuart*, J. Polymer Sci. *34*, 721 (1959).

[101] *B. Seidel*, J. Polymer Sci. *55*, 411 (1961).

[102] *H. Staudinger* and *W. Heuer*, Ber. dtsch. chem. Ges. *63*, 222 (1930).

[103] *L. Valentine*, J. Polymer Sci. *27*, 313 (1958).

[104] *L. Valentine*, Ann. Sci. Text. Belges *4*, 206 (1955).

[105] *H. Zahn*, Palette *2*, 17 (1959).

phthalate) has been fully explained [83,84,85]. The results have been utilized for the interpretation of the spectra of the oligoesters [36,82].

The infrared spectra of the oligoamides, like those of the polyamides, are determined essentially by the vibrations of the amide groups and the CH_2 chains. The bands due to the amide groups have been largely elucidated [86]. By using deuterated nylon 6.6 and deuterated oligoamides from hexamethylenediamine and adipic acid, several bands for methylene groups in α-position to the CO and NH groups have also been recently assigned, along with those for the CO and NH groups [87].

Of special interest in this regard is the deformation vibration at 1435 cm^{-1}, which is produced by skew α-methylene groups. It appears clearly in the higher oligoamides and indicates that these compounds are no longer completely crystalline. The infrared spectra of the higher oligoesters lead to similar conclusions [31].

The reduction of oligoamides to oligoamines can be demonstrated by infrared spectroscopy: the spectra of the oligoamines no longer contain the absorption bands typical of amide groups, but instead, along with intensified CH_2 bands, there is a strong absorption at 1140 to 1130 cm^{-1}, which has been assigned to a C–N stretching vibration [88,89].

VII. X-Ray Studies

X-Ray investigations of the linear and cyclic oligomers discussed in the present work extend essentially to determination and evaluation of powder diagrams in the wide and small angle regions. In addition, the unit cells have been determined for the cyclic oligomers c[B–A]$_2$ [90], c[NH(CH$_2$)$_6$]$_2$ [91], and c[4–h]$_n$ (n = 1, 2) [92].

X-Ray structural analyses of linear oligomers have already been reported in detail [93]. The results discussed in that paper have meanwhile been confirmed by further investigations [27, 44, 59]. It appears from these studies that wide-angle reflections of most oligomers are in good agreement with those of the corresponding polymers. Deviations are seen only for a few initial members of series of homologous oligomers, because these form individual molecular lattices. Apart from these low molecular-weight oligomers, the oligomers crystallize, like the corresponding polymers, in layer or gridiron lattices. However, it must be stated that mixed forms are also observed in several oligoamides, since along with the principal polyamide reflections at about 4.4 and 3.7 Å, there is also a weak interference at about 4.1 Å, which is attributed to a hexagonal structure [94]. Individual oligoamides can be obtained in the hexagonal modification as well as in the monoclinic (*e.g.* nylon 6) or triclinic modifications (*e.g.* nylon 6.6, nylon 6.10).

Small-angle X-ray diagrams have provided interesting results. The long periods determined by such means for linear oligoamides [93] and oligourethanes [95] are directly related to their molecular length up to a calculated chain length of 80 to 100 Å [*]. However, the long periods observed in the preponderant number of cases do not agree with the calculated molecular length, but are generally smaller. This is explained by the assumption that the molecular axis is oblique to the base plane [93,95]. In a few cases, especially among the carboxylic acids and their esters, the long period is larger than the molecular length, but less than twice that length. Thus, it must be assumed that the compounds are associated into double molecules, whose axes are oblique to the base plane. On increasing the chain length beyond the value given above, the long period remains constant; it is therefore independent of chain length, and resembles the reflections discovered in polyamides by *Hess* and *Kiessig* [96]. It has recently been shown that these long periods which are independent of molecular length – just as in the case of the polyamides [96] and polyurethanes [97] – can be extended irreversibly by annealing and reversibly by swelling with phenol solution [13,98]. The X-ray diagrams of annealed samples indicate much sharper, and to some extent additional, reflections; the degree of crystallinity has consequently been increased. The occurrence of the *Hess-Kiessig* reflections in the higher oligomers can be explained by chain folding, thus supporting the theoretical model developed by *Keller* [99] and *Fischer* [100].

Determination of the long periods on unannealed and annealed samples makes it possible to establish which members of a series of homologous oligomers show the Hess-Kiessig reflections in small-angle X-ray patterns, which are independent of molecular weight. These compounds are the transition members to the polymer, *i.e.* the pleionomers. The appearance of this reflection therefore appears suitable for distinguishing the limits between pleionomers and oligomers.

In the cyclic oligomers, the lower members generally have individual lattices. The powder patterns of the higher cyclic oligoamides, on the other hand, show predominantly the same reflections as the corresponding high polymers [57,66, 67]. These compounds also show long periods with lengths which lead to the conclusion that the higher cyclic oligoamides exist as double chains.

Powder patterns of linear oligoamines [27,76,78] show the same reflections as the polyamine gives. In the case of cyclic oligoamines, the long period reflections indicate the existence of extended double chains [76],while with a few linear compounds they agree with the molecular length [27,78].

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[*] Pure oligoesters with molecular lengths of 80 Å and more have not yet been synthetized.

Recent Studies on the Centrally Active Endogenous Amines

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The past five years have witnessed significant progress in our knowledge of the metabolism and importance of endogenous, peripherally and centrally active amines. Most of the modern drugs which influence human mood, emotion, or temperament do so by their direct or indirect effect on the biosynthesis, metabolism, storage, or release of endogenous amines in the brain. The relationships discovered in this connection have deepened our understanding of the biochemical basis of acute, chronic, and hereditary mental disorders. The beginnings of a new science "psychochemistry" are discernible at this point.

I. Introduction

II. Biosynthesis and Metabolism
1. Dopamine
2. Norepinephrine
3. Epinephrine
4. Tyramine
5. Serotonin and Tryptamine
6. Histamine

III. Enzymes controlling the biosynthesis and metabolism of central amines
1. Aromatic hydroxylases and oxidases
2. Decarboxylases
3. Catechol *O*-methyl transferase
4. Amine oxidases
5. Dopamine β-oxidase (norepinephrine synthetase)
6. *N*-Methylases and *N*-acetylases

IV. Distribution and localization of amines and enzymes

V. Interactions of drugs and amines

VI. Interplay of endogenous amines

VII. Endogenous amines in health and disease

VIII. Epilogue: Mental biochemistry and control of the mind

I. Introduction

The field of neurochemistry which lay dormant after the pioneer investigations on the chemical composition of the brain by *Thudichum* has now become a vital discipline. The originally purely descriptive aspects have been developed into a dynamic biochemistry of the brain and its functions. The key compounds in this dynamic biochemistry are the endogenous amines of the central nervous system; their biosynthesis, storage, release and metabolism are reviewed here from the viewpoint of the organic chemist.

II. Biosynthesis and Metabolism

The major biosynthetic route for most amines is decarboxylation of the parent amino acid. The "biogenic amine" (*Guggenheim*) formed may undergo further enzyme-catalysed modifications, such as conjugation, oxidation, methylation, or acetylation, or may be stored, presumably through binding with special sites in proteins. Many of these pathways are reversible or in equilibrium. The pathways involved and their relative importance depend on the amine, on the mode of peripheral administration or central formation, on the presence of drugs, and on the species in which the amine is studied. Some metabolic routes are demonstrable only *in vitro*, others are escape or shunt routes observable *in vivo* after inhibition of the normal metabolic routes. The present survey endeavors to present a broad picture of all potentially possible metabolic pathways [1]. Many amines and their metabolites are excreted in the form of sulfate and glucuronide conjugates. In the interest of brevity and clarity, this aspect of amine metabolism will be disregarded.

1. Dopamine

The metabolism of [^{14}C]dopamine *(1)* in (rats) [2,3] involves mainly deamination (*ca.* 80 %) to homoprotocatechuic acid *(2)* and methylation (20 %) to 3-methoxytyramine *(3)* (Chart 1). The major urinary metabolite is homovanillic acid *(4)*. After treatment with a monoamine-oxidase (MAO-) inhibitor, an unidentified amine is detected as metabolite [2]. Other minor metabolites have been identified as alcohols and *N*-acetyl derivatives [4–6], but their relative physiological importance is difficult to assess at present.

[*] This is an extension of lectures held in Tokyo (Japan) [May, 1961, cf. Kagaku no Ryoiki *15*, 909 (1961)], Basel (Switzerland), and Frankfurt-Hoechst and Ingelheim (Germany) [Summer, 1962], and has been brought into line with the current situation in the field (literature covered up to March, 1963). This review is dedicated to the meritorious editor-in-chief of Angewandte Chemie and connoisseur of literature and the fine arts, *Wilhelm Foerst*, with cordial wishes on the occasion of his 65th birthday.

[1] *J. Axelrod*, Physiol. Rev. *39*, 751 (1959).

[2] *C. M. Williams, A. A. Babuscio*, and *R. Watson*, J. Physiology *199*, 722 (1960).

[3] *M. Goldstein, A. J. Friedhoff*, and *C. Simmons*, Biochim. biophysica Acta *33*, 572 (1959).

[4] *M. Goldstein, A. J. Friedhoff, S. Pomerantz*, and *C. Simmons*, Biochim. biophysica Acta *39*, 189 (1960).

[5] *M. Goldstein, A. J. Friedhoff, S. Pomerantz*, and *J. F. Contrera*, J. biol. Chemistry *236*, 1816 (1961).

[6] *M. Goldstein* and *J. M. Musacchio*, Biochim. biophysica Acta *58*, 607 (1962).

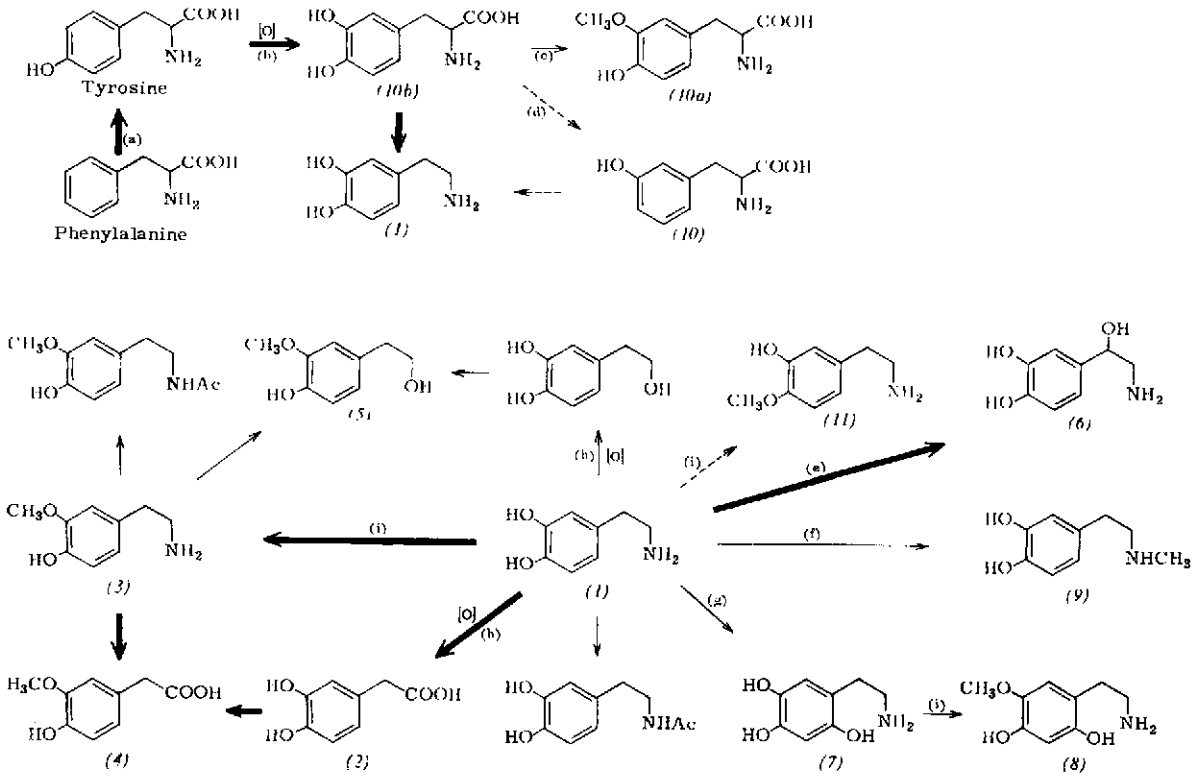


Chart 1. Biosynthesis and metabolism of 3,4-dihydroxyphenethylamine [dopamine, *(1)*].

(a): Phenylalanine hydroxylase
(b): Enzymatic or non-enzymatic hydroxylation (?)
(c): Catechol *O*-methyl transferase
(d): Enzymatic nuclear dehydroxylation (?)
(e): Dopamine β-hydroxylase (non-specific)
(f): In *Bufo marinus*
(g): Non-enzymatic (?)
(h): Monoamine oxidase, alcohol dehydrogenase or aldehyde oxidase
(i): Catechol *O*-methyl transferase
Bold arrows denote main pathways of metabolism.

Brain tissue homogenates (rat) form mainly homoprotocatechuic acid *(2)*, some 3-methoxytyramine *(3)*, an unidentified amine [7], and (3-methoxy-4-hydroxyphenyl)ethanol *(5)* [5] from dopamine *(1)*.

Both side-chain [norepinephrine *(6)*] and nuclear hydroxylation are possible in dopamine. The formation of 2,4,5-trihydroxyphenethylamine *(7)* ("6-hydroxydopamine") occurs readily from dopamine *(1)* either by autoxidation [8] or *via* the hydroxylating system of *Udenfriend* [9]. Amine *(7)* is not only isomeric but also "isographic" (*i.e.* inseparable by regular paper chromatography in many solvent systems) with norepinephrine *(6)*, from which it can be separated after *O*-methylation in the side-chain with anhydrous methanolic hydrogen chloride. It is formed in small amounts *in vivo* (in rats) from [^{14}C]dopamine [8]. The *O*-methylated metabolite of 2,4,5-trihydroxyphenethylamine *(7)*, *viz.* 2,4-dihydroxy-5-methoxyphenethylamine *(8)*, has also been identified after experiments with [^{14}C]dopamine *in vivo* (in rats) [10]. It may correspond to the unidentified amine reported by *Williams* and coworkers [2]. *N*-Methyldopamine *(9)* (epinine) has been discovered for the first time in animals, *viz.* in the parotid glands of the South American toad, *Bufo marinus* [11]. Enhanced amounts of urinary dopamine *(1)* are formed after administration of DL-*m*-tyrosine *(10)* to rats [12]. The excretion of such compounds as 3-methoxytyrosine *(10a)* and dopa *(10b)* [13] in patients with neuroblastoma has diagnostic implications. While conversion of dopamine *(1)* into 10 % (3-hydroxy-4-methoxyphenyl)ethylamine *(11)* and 90 % 3-methoxytyramine *(3)* with catechol-*O*-methyltransferase (COMT) has been observed *in vitro*, *p*-*O*-methylation of dopamine *(1) in vivo* has so far not been established [14].

2. Norepinephrine

The principal urinary metabolites in man of administered norepinephrine *(6)* (see Chart 2) are vanillylmandelic acid, normetanephrine *(12)*, and 3,4-dihydroxymandelic acid *(13)* [15]. In addition, a number of unidentified metabolites are present [15], one of which appears to be vanillic acid *(14)* [16]. (3-Methoxy-4-hy-

[7] *M. Goldstein, A. J. Friedhoff, C. Simmons*, and *N. M. Prochoroff*, Experientia *15*, 254 (1959).

[8] *S. Senoh, C. R. Creveling, S. Udenfriend*, and *B. Witkop*, J. Amer. chem. Soc. *81*, 1768 (1959).

[9] *S. Udenfriend* and *J. R. Cooper*, J. biol. Chemistry *194*, 503 (1952).

[10] *J. W. Daly, L. Horner*, and *B. Witkop*, J. Amer. chem. Soc. *83*, 4787 (1961).

[11] *F. Märki, J. Axelrod*, and *B. Witkop*, Biochim. biophysica Acta *58*, 367 (1962).

[12] *T. L. Sourkes, G. F. Murphy*, and *A. Rabinovitch*, Nature (London) *189*, 577 (1961).

[13] *W. von Studnitz*, Scand. J. clin. Lab. Invest. *12*, Suppl. 48 (1960).

[14] *S. Senoh, J. Daly, J. Axelrod*, and *B. Witkop*, J. Amer. chem. Soc. *81*, 6240 (1959).

[15] *M. Goodall, M. Kirschner*, and *L. Rosen*, J. clin. Invest. *38*, 707 (1959).

[16] *L. Rosen* and *M. Goodall*, Proc. Soc. exp. Biol. Med. *110*, 767 (1962).

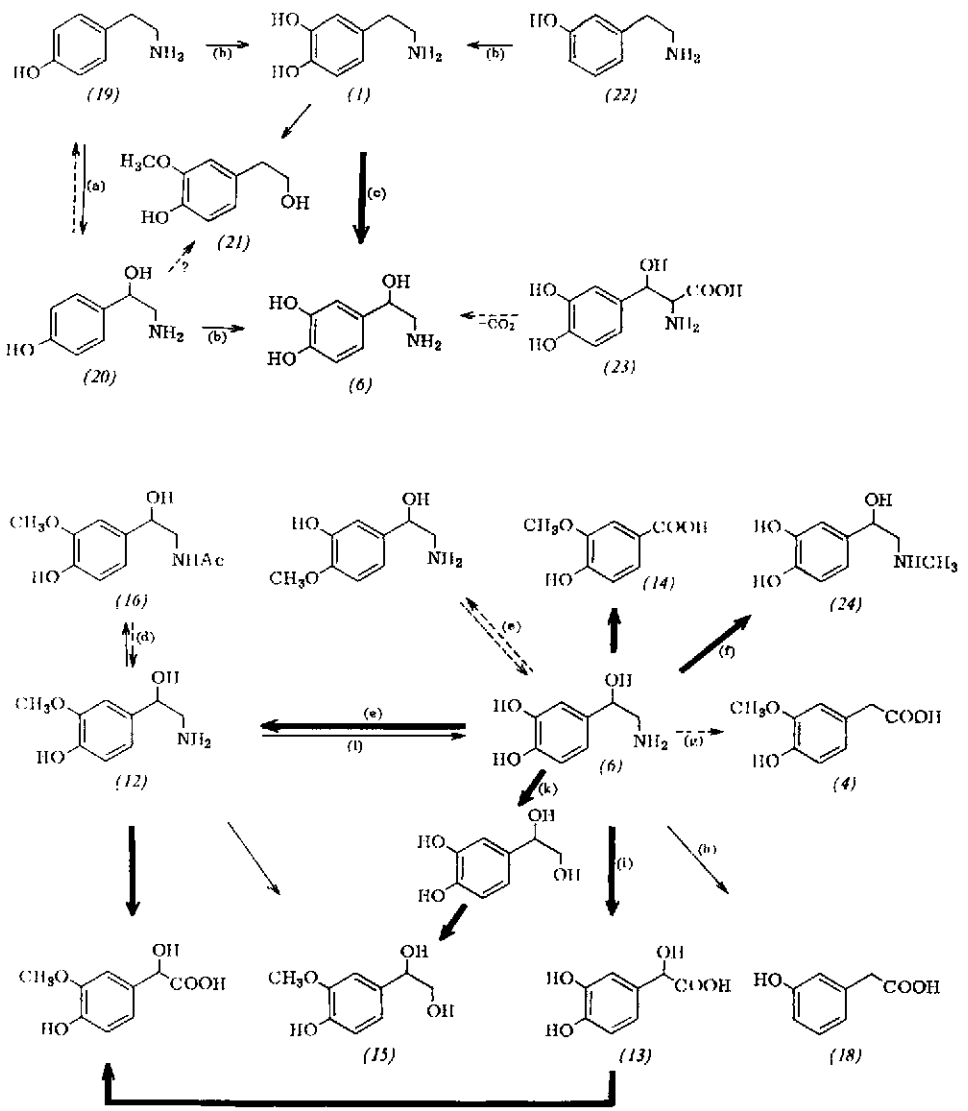
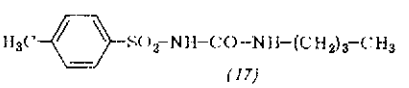


Chart 2. Biosynthesis and metabolism of norepinephrine *(6)*.

(a): Dopamine (phenethylamine) β-oxidase (?)
(b): Non-specific nuclear hydroxylase
(c): Dopamine β-oxidase
(d): Non-specific soluble *N*-acetylase
(e): Catechol *O*-methyl transferase
(f): Non-specific β-phenylethanolamine *N*-methyl transferase
(g): Monoamine oxidase, side-chain dehydroxylation (with tolbutamide)
(h): Side-chain and nuclear dehydroxylation (*via* an intermediate?)
(i): Monoamine oxidase, non-specific aldehyde oxidase
(k): Monoamine oxidase
(l): Non-specific microsomal demethylase
Bold arrows denote main pathways of metabolism.

droxyphenyl)glycol *(15)* appears as a major metabolite in rats [17]. *N*-Acetylnormetanephrine *(16)* [18], a new metabolite, brings to mind the isolation of the sclerotizing substance *N*-acetyldopamine from insects [19]. *N*-Acetyldopamine and possibly *N*-acetylnorepinephrine have been detected in a case of phaeochromocytoma [19a]. Tolbutamide [1-butyl-3-(*p*-tolylsulfonyl)urea] *(17)* specifically directs the metabolism in guinea pigs of norepinephrine *(6)*, dopamine *(1)*, and normetanephrine *(12)* [20] in the direction of homovanillic *(4)* and *m*-hydroxyphenylacetic acid *(18)* [21,22]. The mechanism of this altered metabolism is not known.



(17)

Removal of a phenolic hydroxyl from a catechol derivative in the process of metabolism has been observed previously in rabbits and rats for 3,4-dihydroxyphenylacetic acid [23,24] and protocatechuic acid [25]. Dehydroxylation of phenethanol amines or their metabolites in the side-chain is a novel reaction, and some reservation is in order. For instance, the R_F-values of the two meta-

[17] *J. Axelrod, I. J. Kopin*, and *J. S. Mann*, Biochim. biophysica Acta *36*, 576 (1959).

[18] *A. A. Smith* and *S. B. Wortis*, Biochim. biophysica Acta *60*, 420 (1962); *H. Weissbach, B. G. Redfield*, and *J. Axelrod*, Biochim. biophysica Acta *54*, 190 (1961).

[19] *C. E. Sekeris* and *P. Karlson*, Biochim. biophysica Acta *62*, 103 (1962).

[19a] *C. E. Sekeris* and *P. Herrlich*, Hoppe-Seylers Z. physiol. Chem. *331*, 289 (1963).

[20] *A. Smith, M. Fabrykant, S. Gitlow*, and *S. B. Wortis*, Nature (London) *193*, 577 (1962).

[21] *A. A. Smith*, Biochim. biophysica Acta *69*, 203 (1963).

[22] *A. A. Smith* and *S. B. Wortis*, Fed. Proc. *22*, 388 (1963).

[23] *F. De Eds, A. N. Booth*, and *F. T. Jones*, J. biol. Chemistry *225*, 615 (1957).

[24] *R. R. Scheline, R. T. Williams*, and *J. G. Witt*, Nature (London *188*, 849 (1960).

[25] *J. C. Dacre* and *R. T. Williams*, Biochem. J. *84*, 81P (1962).

bolites given in a preliminary report [20] show poor agreement with those of homovanillic acid and *m*-hydroxyphenylacetic acid. In principle, dehydroxylation of catecholes is the reversal of the hydroxylation: a dihydroxydihydrobenzene derivative may be an intermediate in both processes.

An alternative pathway to norepinephrine *(6)* *via* tyramine *(19)* or octopamine *(20)*, which are both naturally occurring amines [26,27], has been discovered recently [28]. The relative importance of this pathway is unknown. Tyramine *(19)* is oxidized to octopamine *(20)* by the relatively unspecific enzyme dopamine β-oxidase [29]. Ring hydroxylation of octopamine *(20)* to give norepinephrine *(6)* has still to be demonstrated *in vitro*. The situation is complicated by the fact that octopamine *(20)* also forms a phenolic metabolite which is different from norepinephrine *(6)*, which undergoes methylation with COMT, and which is insensitive to the action of periodate – behavior that is indicative of modification of the ethanolamine side-chain *(21)* [30]. Other phenolic amines such as *p*-tyramine *(19)* and *m*-tyramine *(22)* or *N*-methyloctopamine [synephrine, *(31)* in Chart 3] are readily hydroxylated to dopamine *(1)* and epinephrine *(24)*, respectively [31].

Another biosynthesis of norepinephrine *(6)* to be considered is the decarboxylation of 3,4-dihydroxyphenylserine *(23)* [32,33]. However, there are several arguments against this route, *e.g.* 3,4-dihydroxyphenylserine *(23)* is not known to occur naturally, and β-oxidation of amino acids such as tyrosine and dopa *(10b)* cannot be effected by dopamine β-oxidase [34]. It has been reported that a special enzyme in plants can carry out this conversion [35]. In the adrenal gland norepinephrine *(6)* is methylated to epinephrine *(24)* [36].

The initial differences of opinion with regard to the relative importance of MAO and COMT in metabolism have been somewhat reconciled. Peripheral and central metabolism are not necessarily identical. In heart and brain homogenates in which MAO or COMT have been inhibited [37], oxidation of norepinephrine *(6)* by MAO is found to be the major metabolic route. However, in isolated perfused hearts [38,39], *O*-methylation becomes the predominant pathway during active release of norepinephrine. Administered norepinephrine is bound extremely rapidly in tissues [40] and is then released and metabolized slowly. The metabolism of the (unnatural) L-(+)-norepinephrine differs considerably from that of the (natural) D-(−)-norepinephrine [40a].

3. Epinephrine

The metabolic pathways of epinephrine *(24)* (Chart 3) closely resemble those of norepinephrine. Quantitative studies in man of [7-³H]epinephrine of high specific activity have accounted for 97% of the total urinary

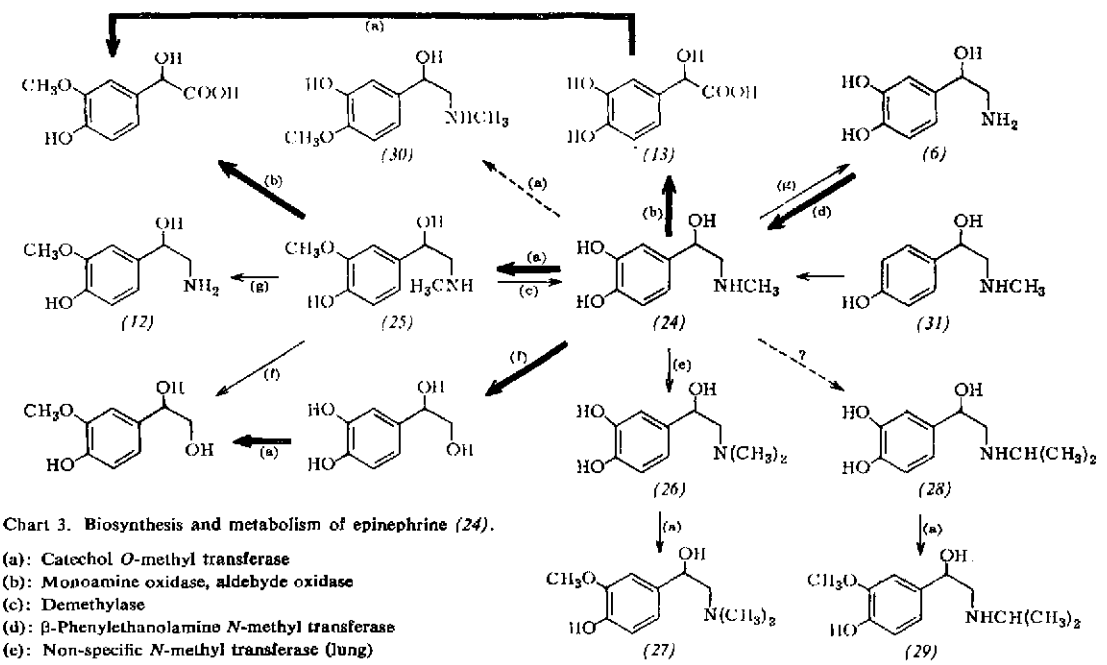


Chart 3. Biosynthesis and metabolism of epinephrine *(24)*.

(a): Catechol *O*-methyl transferase
(b): Monoamine oxidase, aldehyde oxidase
(c): Demethylase
(d): β-Phenylethanolamine *N*-methyl transferase
(e): Non-specific *N*-methyl transferase (lung)
(f): Monoamine oxidase, alcohol dehydrogenase
(g): Non-specific microsomal *N*-demethylase

Bold arrows denote main pathways of metabolism.

[26] *J. B. Jepson, W. Lovenberg, P. Zaltzman, J. A. Oates, A. Sjoerdsma*, and *S. Udenfriend*, Biochem. J. *74*, 5P (1960).

[27] *J. J. Pisano*, Clin. chim. Acta *5*, 406 (1960).

[28] *C. R. Creveling, M. Levitt*, and *S. Udenfriend*, Life Science *1*, 523 (1962).

[29] *J. J. Pisano, C. R. Creveling*, and *S. Udenfriend*, Biochim. biophysica Acta *43*, 566 (1960).

[30] *J. W. Daly* and *J. Axelrod*, unpublished results.

[31] *J. Axelrod*, Science (Washington) *40*, 499 (1963).

[32] *W. J. Hartman, R. S. Pogrund, W. Drell*, and *W. J. Clark*, J. Amer. chem. Soc. *77*, 817 (1955).

[33] *C. G. Schmiterlow*, Brit. J. Pharmacol. Chemotherapy *6*, 127 (1931).

[34] *C. R. Creveling, J. W. Daly, B. Witkop*, and *S. Udenfriend*, Biochim. biophysica Acta *64*, 125 (1962).

[35] *J. E. Gander*, Fed. Proc. *18*, 232 (1959).

[36] *N. Kirschner* and *M. Goodall*, Biochim. biophysica Acta *24*, 658 (1957).

[37] *J. R. Crout, C. R. Creveling*, and *S. Udenfriend*, J. Pharmacol. exp. Therapeut. *132*, 269 (1961).

[38] *I. J. Kopin, G. Hertting*, and *E. K. Gordon*, J. Pharmacol. exp. Therapeut. *138*, 34 (1962).

[39] *C. A. Chidsey, R. L. Kahler, L. L. Kelminson*, and *E. Braunwald*, Circulation Res. *12*, 220 (1963).

[40] *L. G. Whitby, J. Axelrod*, and *H. Weil-Malherbe*, J. Pharmacol. exp. Therapeut. *132*, 193 (1961).

[40a] *I. J. Kopin* and *W. Bridgers*, Life Science *2*, 356 (1963).

radioactivity in forms of known metabolites [41]. The extent of biliary excretion depends on the mode of infusion, *viz.* 10 % by intrajugular or 31 % by intraportal infusion, and follows a similar pattern [42]. An elegant method using double-labelling techniques has been developed for assessing the relative importance of 3-*O*-methylation and deamination of epinephrine *(24)* in man [43,44]. Initial methylation accounted for 70 % of the metabolism of infused epinephrine, while the remainder first underwent deamination. As with norepinephrine, glycols were major metabolites in the rat and only minor ones in humans [17,45]. In cats, [2-^{14}C]-epinephrine was converted into urinary metanephrine *(25)* and substituted mandelic acids and glycols besides three unidentified acidic or neutral compounds and one unidentified amine [46]. The amine was a major metabolite (35 %) when both MAO and COMT were inhibited *in vivo* or in tissue homogenates [47].

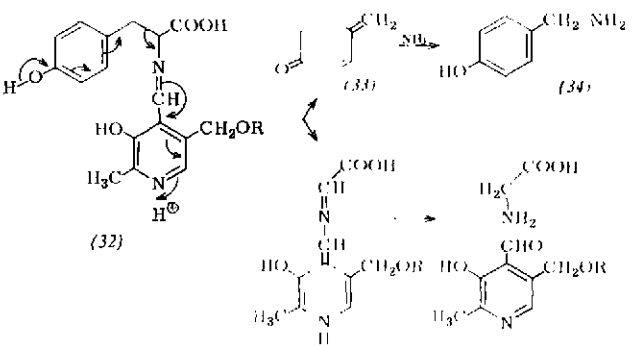
Enzymatic *N*-demethylation of metanephrine *(25)* to normetanephrine *(12)* has been demonstrated in rabbit liver preparations but has still to be demonstrated *in vivo* [48]. The analogous conversion of [7-^{3}H]epinephrine *(24)* into norepinephrine *(6)* in cats has been claimed [49]. Methylation of epinephrine *(24) in vitro* leads to the tertiary amine *(26)*, a compound which occurs normally in adrenal glands [50]. Its 3-*O*-methyl derivative, *N*-methylmetanephrine *(27)*, occurs in human urine [51], especially from patients suffering from pheochromocytoma tumors [51] and from juvenile psychotics [52].

A compound with properties resembling those of isoproterenol *(28)* (*N*-isopropylnorepinephrine), which is reported to occur in adrenal glands [53], has now been claimed to be present in the blood of cats following injection of epinephrine; norepinephrine gave negative results [54]. These findings have not been confirmed in other laboratories. Isoproterenol *(28)* itself is metabolized to its 3-*O*-methyl ether *(29)* in humans [51].

Enzymatic *p*-*O*-methylation [formation of paranephrine *(30)*] occurs to the extent of 10 % with epinephrine *(24) in vitro* but not *in vivo* [55]. Microsomal *O*-demethylases reconvert metanephrine *(25)* into epinephrine *(24) in vitro* [56] as well as *in vivo* [44]. The initial pattern of disappearance of infused epinephrine depends on the mode and extent of "binding" [57].

4. Tyramine

Tyramine *(19)* (Chart 4) is formed from tyrosine *(30a)* by the action of the non-specific enzyme *aromatic amino-acid decarboxylase* [58]. This decarboxylation proceeds via a pyridoxylidene intermediate *(32)* [59]. Such an intermediate could also undergo cleavage by a reverse Michael reaction to form a reactive quinone methine *(33)* which could add on ammonia (or amines) to give *p*-hydroxybenzylamine *(34)*, a normal constituent of human urine [60]. This hypothetical mechanism is analogous to the one proposed for the direct formation of gramine from tryptophan in plants [61,62].



α-Hydroxylation of tyramine *(19)* to octopamine *(20)* [29], or of *m*-tyramine *(22)* to *m*-octopamine *(35)* [34], or of dopamine *(1)* to norepinephrine *(6)* is mediated by a non-specific enzyme called dopamine β-oxidase (or norepinephrine synthetase) which has recently been solubilized [63]. *m*-Tyramine *(22)* [60], octopamine *(20)* [29,60], and *N*-methyloctopamine *(31)* (synephrine) [60,64] are normal constituents of human urine. The identification of *N*-methyltyramine *(36)* in normal human urine is tentative [60]. A non-specific acetylase converts amines – including tyramine *(19)* – into *N*-acetyl derivatives *(37)* [18,19]. The various amines are substrates of MAO [65], and the resulting acids *(18)*, *(37a)*, and *(37b)* (Chart 4) are normal constituents of human urine [66].

[41] *E. H. LaBrosse, J. Axelrod, I. J. Kopin,* and *S. S. Kety,* J. clin. Invest. *40,* 253 (1961).

[42] *G. Hertting* and *E. H. LaBrosse,* J. biol. Chemistry *237,* 2291 (1962).

[43] *I. J. Kopin,* Science (Washington) *131,* 1372 (1960).

[44] *I. J. Kopin, J. Axelrod,* and *E. Gordon,* J. biol. Chemistry *236,* 2109 (1961).

[45] *I. J. Kopin* and *J. Axelrod,* Arch. Biochem. Biophysics *89,* 148 (1960).

[46] *N. Kirshner, L. Terry,* and *D. D. Pollard,* Arch. int. Pharmacodynam. Thérap. *133,* 421 (1961).

[47] *A. F. De Schaepdryver* and *N. Kirshner,* Arch. int. Pharmacodynam. Thérap. *133,* 433 (1961).

[48] *J. Axelrod,* Experientia *16,* 502 (1960).

[49] *W. G. Verly, G. Koch,* and *G. Hunbelle,* Arch. int. Physiol. Biochim. *70,* 624 (1962).

[50] *J. Axelrod,* Biochim. biophysica Acta *45,* 614 (1960).

[51] *C. Itoh, K. Yoshinaga, T. Sato, N. Ishida,* and *Y. Wada,* Nature (London) *193,* 477 (1962); *R. Robinson* and *P. Smith,* Clin. chim. Acta *7,* 29 (1962).

[52] *T. L. Perry,* Science (Washington) *139,* 587 (1963).

[53] *M. F. Lockett,* Brit. J. Pharmacol. Chemotherapy *9,* 498 (1954).

[54] *K. E. Eakins* and *M. F. Lockett,* Brit. J. Pharmacol. Chemotherapy *16,* 108 (1961).

[55] *J. W. Daly, J. Axelrod,* and *B. Witkop,* J. biol. Chemistry *235,* 1155 (1960).

[56] *J. Axelrod* and *S. Szara,* Biochim. biophysica Acta *30,* 188 (1958).

[57] *J. Axelrod, H. Weil-Malherbe,* and *R. Tomchick,* J. Pharmacol. exp. Therapeut. *127,* 151 (1959).

[58] *W. Lovenberg, H. Weissbach,* and *S. Udenfriend,* J. biol. Chemistry *237,* 89 (1962).

[59] S. *Mandeles, R. Koppelman,* and *M. E. Hanke,* J. biol. Chemistry *209,* 327 (1954).

[60] *Y. Kakimoto* and *M. D. Armstrong,* J. biol. Chemistry *237,* 208 (1962).

[61] *E. Wenkert,* J. Amer. chem. Soc. *84,* 98 (1962).

[62] *D. O'Donovan* and *E. Leete,* J. Amer. chem. Soc. *85,* 461 (1963).

[63] *E. Y. Levin, B. Levenberg,* and *S. Kaufman,* J. biol. Chemistry *235,* 2080 (1960).

[64] *J. J. Pisano, J. A. Oates Jr., A. Karmen, A. Sjoerdsma,* and *S. Udenfriend,* J. biol. Chemistry *236,* 898 (1961).

[65] *H. Blaschko,* Pharmacol. Rev. *4,* 415 (1952).

[66] *M. D. Armstrong, K. M. F. Shaw,* and *P. E. Wall,* J. biol. Chemistry *218,* 293 (1956).

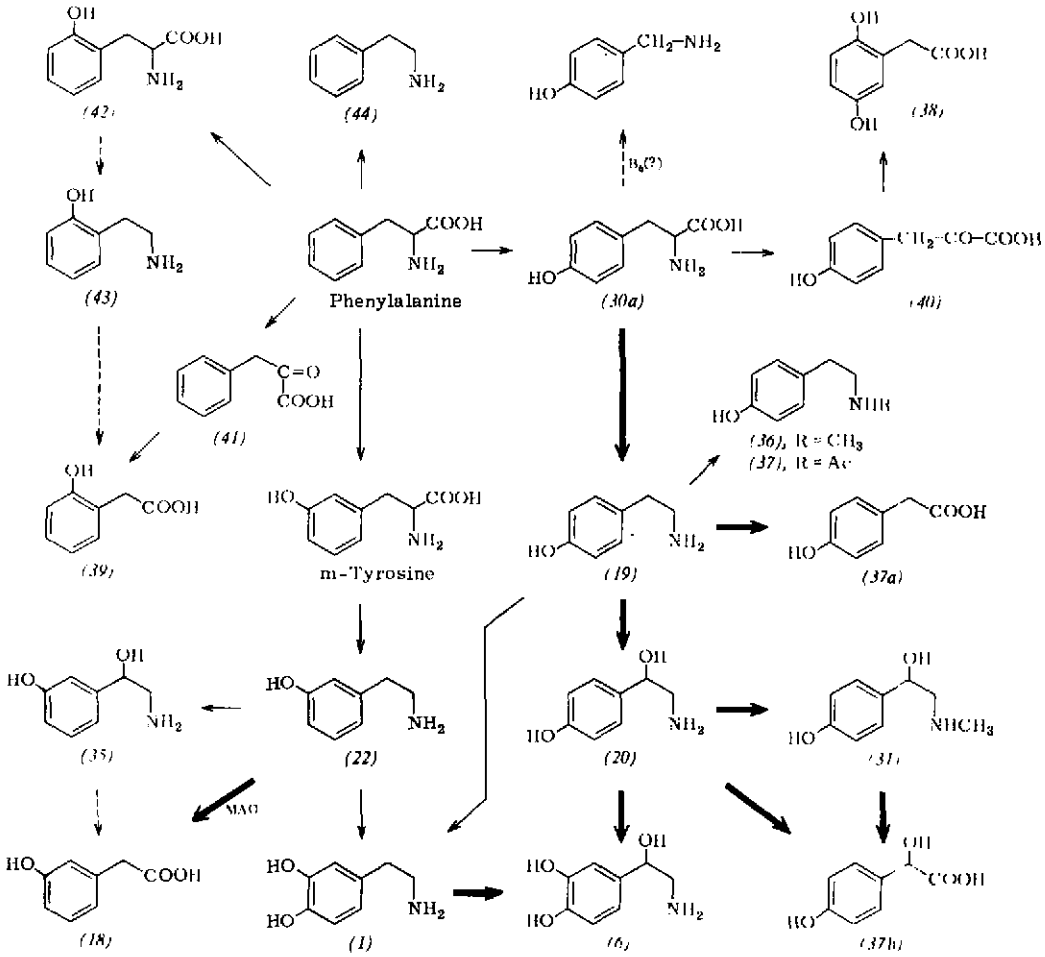
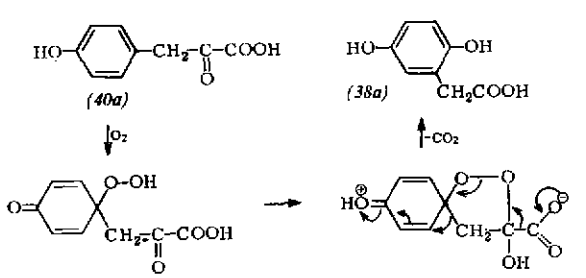
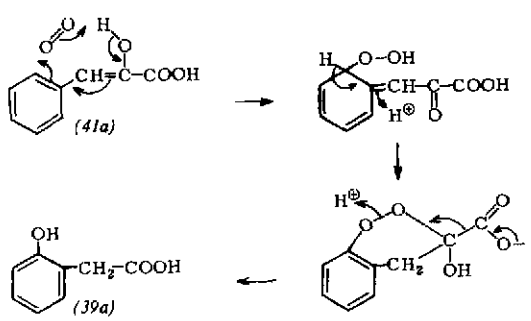


Chart 4. Biosynthesis of tyramine *(19)* and metabolism of tyramine*(19)*, tyrosine *(30a)*, and phenylalanine.

Homogentisic *(38)* and *o*-hydroxyphenylacetic acid *(39)* in urine [66] or blood [67] result from the action of the enzyme *p*-hydroxyphenylpyruvic acid oxidase on *p*-hydroxyphenylpyruvic acid *(40)* and phenylpyruvic acid *(41)* [68,69], respectively. Any mechanism for the formation of homogentisic acid [*(40a)* → *(38a)*] such as the one suggested previously [70] must explain the facts that hydroxylation, decarboxylation, and migration of the side chain are catalysed by a single enzyme and that there is no indication for the existence of an intermediate. A different mechanism explaining the formation of *o*-hydroxyphenylacetic from phenylpyruvic acid



[*(41a)* → *(39a)*] depicts *ortho*-oxidation and decarboxylation without migration of the side chain. The latter point is under investigation.



The alternative formation of *o*-hydroxyphenylacetic acid *(39)* from *o*-tyrosine *(42)* *via* *o*-tyramine *(43)* is probably a minor metabolic route [71]. Phenethylamine *(44)* is a significant metabolite in phenylketonurics [72]. Tyramine *(19)* functions both as a precursor of [28], as well as releasing agent for, norepinephrine *(6)* from binding sites [73].

[67] *J. M. Hicks, D. S. Young*, and *I. D. P. Wooton*, Clin. chim. Acta *7*, 623 (1962).

[68] *S. E. Hager, R. I. Gregerman*, and *W. E. Knox*, J. biol. Chemistry *225*, 935 (1957).

[69] *K. Taniguchi* and *M. D. Armstrong*, Fed. Proc. *22*, 296 (1963).

[70] *S. Goodwin* and *B. Witkop*, J. Amer. chem. Soc. *79*, 179 (1956).

[71] *J. B. Jepson, W. Lovenberg, A. Sjoerdsma, J. A. Oates, P. Zaltzman*, and *S. Udenfriend*, The Pharmacologist *1*, No. 2, p. 74, fall of 1959.

[72] *J. A. Oates, P. Z. Nirenberg, J. B. Jepson, A. Sjoerdsma*, and *S. Udenfriend*, Proc. Soc. exp. Biol. Med., *112*, 1078 (1963).

[73] *J. Burn* in *J. R. Vane, G. E. W. Wolstenholme*, and *M. O'Connor*: Adrenergic Mechanisms. Little Brown & Co., Boston 1960.

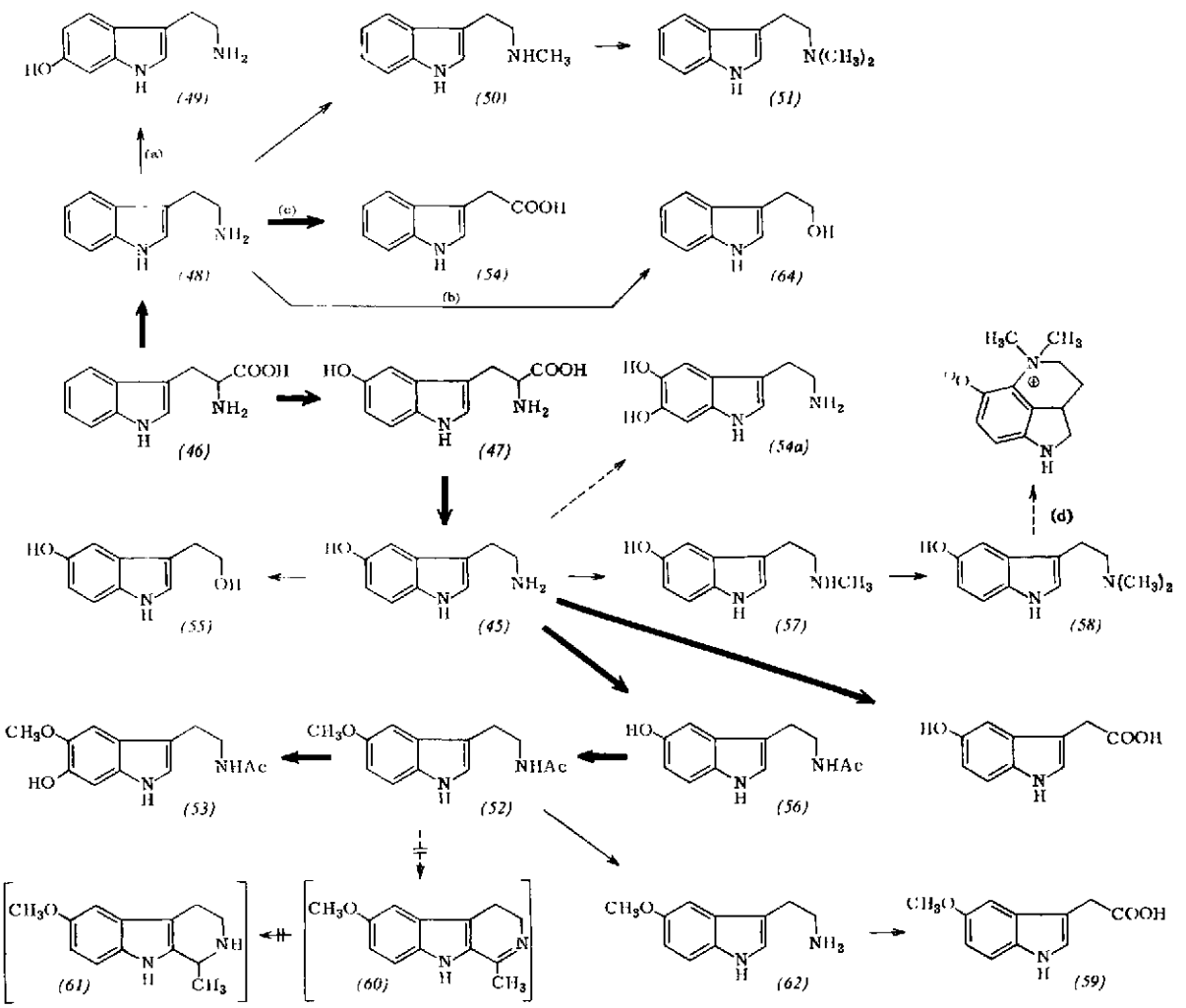


Chart 5. Biosynthesis and metabolism of serotonin *(45)* and tryptamine *(48)*.

(a): Microsomal hydroxylase
(b): In rats after treatment with disulfiram *(63)*
(c): Monoamine oxidase
(d): In *Bufo marinus*
Bold arrows denote main pathways of metabolism.

5. Serotonin and Tryptamine

Conversion of tryptophan *(46)* into serotonin *(45)* (Chart 5) involves two steps: hydroxylation to give 5-hydroxytryptophan *(47)* and decarboxylation by aromatic amino-acid decarboxylase [58]. The alternative pathway of tryptamine *(48)* to serotonin *(45)* has been ruled out [74], although hydroxylation of tryptamine *(48)* in the 6-position *(49)* can be effected by enzymes present in liver microsomes [75]. 6-Hydroxylation of indoles is very common and, in addition to tryptamine *(48)*, α-methyltryptamine *(50)* [76], dimethyltryptamine *(51)* [77], skatole [78,79], melatonin *(52)* → *(53)* [80], and indole-3-acetic acid *(54)* [75] all undergo 6-hydroxylation *in vivo* or *in vitro*.

Little is known about the enzyme which hydroxylates tryptophan *(46)*. Its isolation from intestines of rats and guinea pigs has been claimed [81]. Non-enzymatic hydroxylation may have occurred under the conditions described as requirements for this "enzyme". Phenylalanine hydroxylase from liver can also effect hydroxylation of tryptophan *(46)* [82], but this enzyme is of little significance in the formation of serotonin *(45)* *in vivo*.

The metabolism of serotonin *(45)* involves oxidative deamination (MAO), acetylation, or conjugation [83]. The mode and dose of administration effects the metabolism of serotonin as it does that of catecholamines [1]. The body responds to large doses chiefly by causing conjugation; smaller, more physiological doses are oxidatively deaminated [84]. The evidence for the occurrence of a serotonin metabolite with the properties of a catechol derivative is not complete [83]. Such a compound would be of interest since 5,6-dihydroxytryptamine

[74] *S. Udenfriend, C. R. Creveling, H. Posner, B. G. Redfield, J. Daly*, and *B. Witkop*, Arch. Biochem. Biophysics *83*, 501 (1959).

[75] *J. B. Jepson, P. Zaltzman*, and *S. Udenfriend*, Biochim. biophysica Acta *62*, 91 (1962).

[76] *S. Szara*, Experientia *17*, 76 (1961).

[77] *S. Szara* and *J. Axelrod*, Experientia *15*, 216 (1959).

[78] *E. C. Horning, C. C. Sweeley, C. E. Dalgliesh*, and *W. Kelly*, Biochim. biophysica Acta *32*, 566 (1959).

[79] *R. M. Acheson* and *A. R. Hands*, Biochim. biophysica Acta *51*, 579 (1961).

[80] *I. J. Kopin, C. M. B. Pare, J. Axelrod*, and *H. Weissbach*, J. biol. Chemistry *236*, 3072 (1961).

[81] *J. R. Cooper* and *I. Melcer*, J. Pharmacol. exp. Therapeut. *132*, 265 (1961).

[82] *J. Renson, H. Weissbach*, and *S. Udenfriend*, J. biol. Chemistry *237*, 2261 (1962).

[83] *W. M. McIsaac* and *I. H. Page*, J. biol. Chemistry *234*, 858 (1959).

[84] *M. M. Airaksinen*, Biochem. Pharmacol. *8*, 245 (1961).

(54a) is a neurohormone in crustacea [85] and possibly in insects [86]. Such dihydroxyindoles undergo *O*-methylation non-specifically with COMT from liver, or specifically with hydroxyindole *O*-methyl transferase from pineal gland [87,88]. In the reaction of 5,6-dihydroxyindoles with 5-hydroxyindole *O*-methyl transferase, 90 % of the methylation occur at the 5- and only 10 % at the 6-position. For COMT, the values are 30 and 70 %, respectively.

5-Hydroxytryptophol *(55)* is a metabolite of serotonin *(45)* in rats [89]. Because of its similar chromatographic properties to *N*-acetylserotonin *(56)*, earlier reports [83,90] on the occurrence of *N*-acetylserotonin must be re-evaluated. A similar difficulty exists for *N*-acetyldopamine and other dopamine metabolites.

Serotonin *(45)* and tryptamine *(48)* are *N*-methylated to the secondary amines *(57)* and *(50)* and even to the tertiary amines *(58)* and *(51)* by a non-specific *N*-methylase from rabbit lung [91]. This finding is of special interest, because bufotenine *(58)* (*N,N*-dimethylserotonin) [92] and *N,N*-dimethyltryptamine *(51)* [93] are psychotomimetic agents.

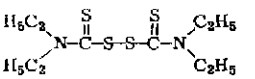
Acetylation of serotonin *(45)* [18] followed by *O*-methylation [88] results in a potent melanocyte-contracting substance, melatonin *(52)*, which is found in bovine pineal glands [94]. Melatonin *(52)* is metabolized *via* 6-hydroxylation *(53)* [80,95]. In addition, small amounts of 5-methoxyindole-3-acetic acid *(59)* and one or two metabolites which do not give a typical indole reaction with Ehrlich's reagent are obtained. It has been proposed that one of these compounds might be identical with 10-methoxyharmalan *(60)*, a potent serotonin antagonist [96], which could result from cyclodehydration of melatonin *(52)*. No evidence for positive identification of the non-indolic metabolites of melatonin has been published.

It has also been claimed [97] that a fluorescent compound from beef pineal tissue which stimulates secretion of aldosterone, *viz.* adrenoglomerulotropin [98], is identical with a reduction product of 10-methoxyharmalan *(60)*, *viz.* 1-methyl-6-methoxy-1,2,3,4-tetrahydro-2-carboline *(61)*, which arises by condensation of 5-methoxytryptamine *(62)* with acetaldehyde *in vivo* [99]. However, subsequent testing of this carboline *(61)* gave erratic results [100]. In this laboratory [101], we were unable to detect 1-methyl-6-methoxy-1,2,3,4-tetrahydro-2-carboline in beef pineal glands using an extremely sensitive fluorimetric assay. Furthermore, the compound showed only a low order of adrenoglomerulotropic activity in contrast to the original report [97].

5-Methoxytryptamine *(62)* has pharmacological properties similar to serotonin *(45)* in some systems [102, 103] and has been claimed to be present in the urine of rheumatic patients [104]. The amine is metabolized mainly by oxidation to 5-methoxyindole-3-acetic acid *(59)* [95].

Again, the process of "binding" is important in the initial stages of metabolism and disposition of infused serotonin *(45)* [105].

Tryptamine *(48)* arising by decarboxylation of tryptophan *(46)* [106] is mainly oxidatively deaminated by MAO [90]. In addition to indole-3-acetic acid *(54)*, the alcohol tryptophol *(64)* appears as a major metabolite of tryptamine in rats treated with disulfiram *(63)* [107].



(63)

6. Histamine

Histamine *(65)* [108] arises from histidine *(66)* by decarboxylation by the action of either the non-specific aromatic L-amino-acid decarboxylase [58] or of the specific histidine decarboxylase of mast cells [109] (Chart 6). Complete inhibition of the non-specific decarboxylase has no effect on histamine excretion [109]. Thus it seems to have little physiological importance in the normal biosynthesis of histamine.

Histamine *(65)* may be deaminated either by the physiologically important diamine oxidase or MAO [108]. In both cases, imidazolylacetic acid *(67)* is formed. A second method of the physiological inactivation of histamine *(65)* involves *N*-methylation by a specific histamine *N*-methyl transferase [110] leading to 1-methylhistamine *(68)*. The occurrence of 3-methylhistamine *(69)* has been reported after administration of large amounts of histamine [111]. However, with physiological

[85] *D. B. Carlisle*, Biochem. J. *63*, 32P (1956).

[86] *K. J. Davey*, Canad. J. Zool. *38*, 39 (1960).

[87] *J. Axelrod* and *A. B. Lerner*, Biochim. biophysica Acta, in the press.

[88] *J. Axelrod* and *H. Weissbach*, J. biol. Chemistry *236*, 211 (1961).

[89] *S. Kreder*, *S. Iskrić*, and *D. Keglević*, Biochem. J. *85*, 447 (1962).

[90] *H. Weissbach*, *W. Lovenberg*, *B. C. Redfield*, and *S. Udenfriend*, J. Pharmacol. exp. Therapeut. *131*, 26 (1961).

[91] *J. Axelrod*, J. Pharmacol. exp. Therapeut. *138*, 28 (1962).

[92] *H. D. Fabing* and *J. R. Hawkins*, Science (Washington) *123*, 886 (1956).

[93] *S. Szara*, Experientia *12*, 441 (1956).

[94] *A. B. Lerner*, *J. D. Case*, and *Y. Takahashi*, J. biol. Chemistry *235*, 1992 (1960).

[95] *S. Kveder* and *W. M. McIsaac*, J. biol. Chemistry *236*, 3214 (1961).

[96] *W. M. McIsaac*, *P. A. Khairallah*, and *I. H. Page*, Science (Washington) *134*, 674 (1961).

[97] *G. Farrell* and *W. M. McIsaac*, Arch. Biochem. Biophysics *94*, 543 (1961).

[98] *G. Farrell*, Endocrinology *65*, 239 (1959).

[99] *W. M. McIsaac*, Biochim. biophysica Acta *52*, 607 (1961).

[100] *A. M. Taylor*, *W. M. McIsaac*, and *G. Farrell*, Fed. Proc *21*, 186a (1962).

[101] *F. Märki* and *B. Witkop*, unpublished results.

[102] *R. Michaux*, Life Science *1*, 617 (1962).

[103] *A. Cession-Fossion* and *R. Michaux*, Life Science *1*, 483 (1962).

[104] *C. H. Haddox Jr.* and *M. S. Saslaw*, unpublished results.

[105] *J. Axelrod* and *J. K. Inscoe*, J. Pharmacol. exp. Therapeut., in the press.

[106] *H. Weissbach*, *W. King*, *A. Sjoerdsma*, and *S. Udenfriend*, J. biol. Chemistry *234*, 81 (1959).

[107] *A. A. Smith* and *S. B. Wortis*, Biochim. biophysica Acta *40*, 569 (1960).

[108] *R. W. Shayer*, Physiol. Rev. *39*, 116 (1959).

[109] *H. Weissbach*, *W. Lovenberg*, and *S. Udenfriend*, Biochim. biophysica Acta *50*, 177 (1961).

[110] *D. D. Brown*, *J. Axelrod*, and *R. Tomchick*, Nature (London) *183*, 680 (1959); cf. *A. Gustafsson* and *G. P. Forshell*, Acta chem. scand. *17*, 541 (1963).

[111] *S. A. Karjala* and *B. W. Turnquest*, J. Amer. chem. Soc. *77*, 6358 (1955).

amounts, only 1-methylhistamine *(68)* and 1-methylimidazol-4-ylacetic acid *(70)* are formed [112]. *N*-Acetylation[113], *N*-monomethylation, and *N,N*-dimethylation of the primary amino group of histamine occur as metabolic processes forming *(71)*, *(72)*, and *(73)*, respectively [114]. Histamine arising endogenously from histidine is bound, but not exogeneous histamine [115].

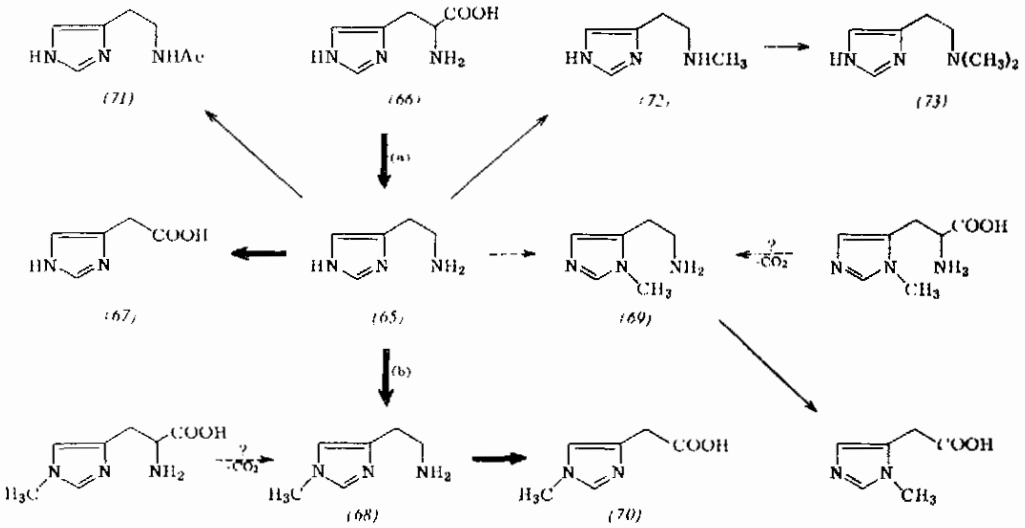


Chart 6. Biosynthesis and metabolism of histamine *(65)*.
(a): Specific histidine decarboxylase (mast cells) or (non-specific) aromatic L-amino-acid decarboxylase
(b): Specific *N*-methylase
Bold arrows denote main pathways of metabolism.

III. Enzymes Controlling the Biosynthesis and Metabolism of Central Amines

Decarboxylation, hydroxylation, *O*-methylation, oxidative deamination, *N*-methylation, and *N*-acetylation are common reactions in amine metabolism (Chart 7). The isolation and study of the enzymes concerned with these transformations contribute to our understanding of the dynamic pattern of intermediary metabolism. However, it must be realized that in the functioning cell or organism, other factors, such as active transport and membrane permeability and their special regulators, are of an importance which is hard to overestimate. The following section will survey some of the investigations on enzymes concerned with the biosynthesis and metabolism of pharmacodynamic amines.

1. Aromatic Hydroxylases and Oxidases

Recent reviews [116–118] cover many aspects of hydroxylation and oxidation as related to biological amines.

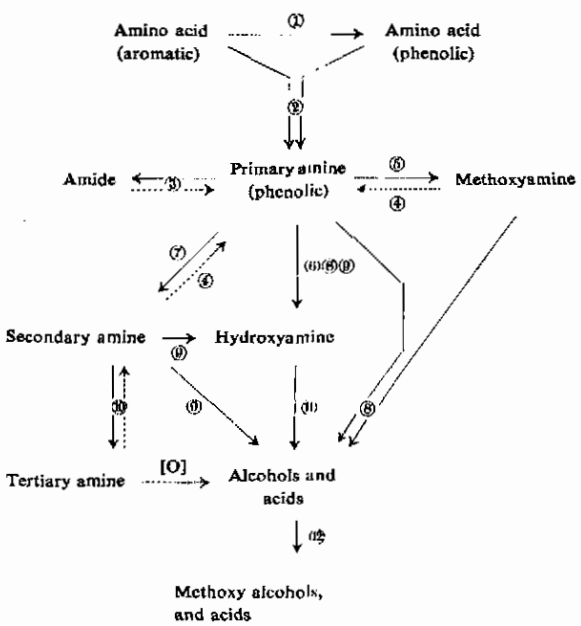


Chart 7. Interrelationships of enzymes and substrates
1: Phenylalanine hydroxylase (non-specific)
2: Aromatic amino-acid decarboxylase (non-specific)
3: *N*-Acetylase (non-specific)
4: Microsomal demethylases (non-specific)
5: Specific and non-specific *O*-methyl transferases
6: Nuclear or side-chain hydroxylation
7: Specific and non-specific *N*-methyl transferases
8: Phenethylamine hydroxylase (non-specific)
9: Catechol- or monophenol-forming hydroxylases
10: Non-specific *N*-methyl transferases (lung)
11: Monoamine oxidase
12: *O*-Methyl transferases (non-specific)

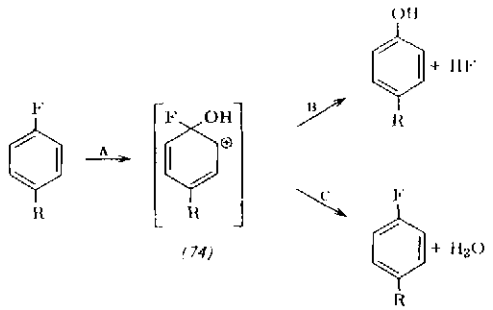
The enzyme phenylalanine hydroxylase which occurs in the soluble fraction of liver, requires a cofactor, probably a tetrahydropteridine derivative, which is oxidized to a "dihydropteridine" during the formation of tyrosine from phenylalanine. Another enzyme, a TPNH dehydrogenase [*] is usually isolated from sheep liver and is required for coupling the reduction of the

[112] *R. W. Schayer* and *S. A. Karjala*, J. biol. Chemistry *221*, 307 (1956).
[113] *H. Tabor* and *E. Mosettig*, J. biol. Chemistry *180*, 703 (1949).
[114] *R. Kapeller-Adler* and *B. Iggo*, Biochim. biophysica Acta *25*, 394 (1957).
[115] *R. W. Schayer*, J. biol. Chemistry *199*, 245 (1952).
[116] *H. S. Mason*, Advances in Enzymol. *19*, 79 (1957).
[117] *K. Massart* and *R. Vercanteren*, Ann. Rev. Biochem. *28*, 527 (1959).
[118] *O. Hayaishi*, Ann. Rev. Biochem. *31*, 25 (1962).

[*] TPNH = reduced triphosphopyridine nucleotide. TPN = triphosphopyridine nucleotide.

cofactor to the oxidation of TPNH [119–120]. The strucutre of the cofactor has been adduced from colorimetric and fluorimetric characteristics, inhibition of the enzyme by folic acid antagonists, and replacement of the cofactor by such highly active compounds as 2-amino-4-hydroxy-6,7-dimethyl-5,6,7,8-tetrahydropteridine [120]; the latter also facilitated studies on species and tissue distribution of phenylalanine hydroxylase [121]. The inactivation of the enzyme after incubation with versene or cysteine can be reversed with ferrous ion [119], but it is not known whether a metal ion cofactor is required.

The enzyme utilizes O_2 and not H_2O as the source of oxygen in the conversion of phenylalanine into tyrosine [122] and also catalyses the oxidative conversion of 4-fluorophenylalanine into tyrosine [123]; this latter reaction was postulated to involve an intermediate *(74)* which is



either reductively deoxygenated (pathway C) to 4-fluorophenylalanine or reductively defluorinated (pathway B) to tyrosine. The evidence for this was the high ratio of TPN to tyrosine formation. Pathways B and C both lead through the tetrahydropteridine cofactor to TPN, but tyrosine arises only *via* A and B. Whether the natural substrate, phenylalanine, goes through a similar reversible intermediate is not known. Preliminary studies on this enzyme and acetanilide hydroxylase [124] from rabbit liver microsomes did not provide evidence for an activated intermediate containing exchangeable hydrogen, but the results were not definitive [125]

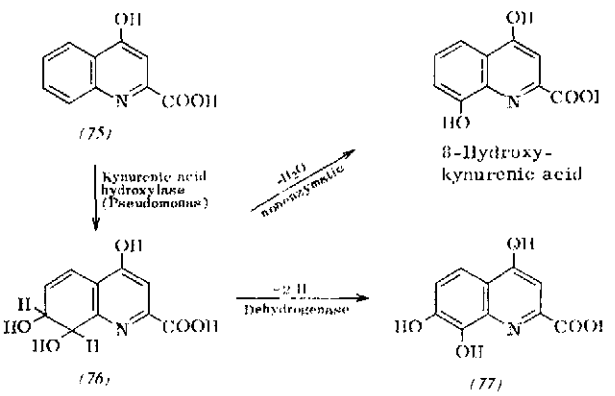
Isolation of the enzyme tryptophan 5-hydroxylase from the particulate fraction of small intestines and kidney [81] could not be repeated by *Hayaishi* and *Udenfriend* [125a]. The characterization and inhibition of this hydroxylase are still unsolved problems.

Nonspecific microsomal hydroxylases in liver [116] hydroxylate indoles [75–80] and aromatic compounds [126].

Catechols are formed from phenols by the action of the enzyme tyrosinase, a mixed-function oxidase [116] which hydroxlates tyrosine and oxidizes dopa to dopa quinone and further to melanin. Tyrosinase-catalysed hydroxylation of tritiated 3,4-dimethylphenol exhibits a very small isotope effect [127] indicative of an electrophilic substitution of an activated ring. An enzyme, not tyrosinase, forms dopa from tyramine in insects [19].

Dopa also arises by non-enzymatic hydroxylation from tyrosine [128] in the ascorbic acid-H_2O_2-versene system [9]. Catecholamines may arise from phenolic amines. Examples are dopamine *(1)* from *p*-tyramine *(19)* and *m*-tyramine *(22)* or epinephrine *(24)* from *N*-methyloctopamine *(31)* [31].

The precursors of catechols may be dihydrodiol intermediates. Such an unstable diol *(76)* has been isolated as the precursor of 7,8-dihydroxykynurenic acid *(77)* from kynurenic acid *(75)* [129]. Enzymes which catalyse dehydrogenations of dihydrodiols exist in mammalian tissues [130]. Dihydrodiols and phenols may result from a common (epoxide-like?) intermediate during microsomal hydroxylation [131]. Such dihydrodiol derivatives could, in principle, also be postulated as intermediates in the dehydroxylation of catechols to phenols [21–25].



Enzymes which catalyse the oxidation of hydroxyindoles to quinone-like products include *Mytilus* gill plate enzyme [132], mammalian caeruloplasmin [133], and cytochrome oxidase [134]. Caeruloplasmin [135] and cytochrome oxidase [136] also oxidize catecholamines to aminochromes. The nature of this reaction has been investigated with the aid of spectrophotometry and electron spin resonance [137]. An

[119] *S. Kaufman*, J. biol. Chemistry *234*, 2677 (1959).

[120] *S. Kaufman* and *B. Levenberg*, J. biol. Chemistry *234*, 2683 (1959).

[121] *P. J. Christenson*, Scand. J. clin. Lab. Invest. *14*, 623 (1962).

[122] *S. Kaufman, W. F. Bridgers, F. Eisenberg*, and *S. Friedman*, Biochem. biophys. Res. Commun. *9*, 497 (1962).

[123] *S. Kaufman*, Biochim. biophysica Acta *51*, 619 (1961).

[124] *C. Mitoma, H. S. Posner, H. C. Reitz*, and *S. Udenfriend*, Arch. Biochem. Biophysics *61*, 431 (1956).

[125] *C. Chidsey, J. Daly, Y. Kanaoka, B. Witkop*, and *S. Udenfriend*, unpublished results.

[125a] *O. Hayaishi* and *S. Udenfriend*, personal communication.

[126] *C. Mitoma, H. S. Posner, H. C. Reitz*, and *S. Udenfriend*, Arch. Biochem. Biophysics *61*, 431 (1956); *H. S. Posner, C. Mitoma*, and *S. Udenfriend*, ibid. *94*, 269 (1961).

[127] *B. J. Wood* and *L. L. Ingraham*, Arch. Biochem. Biophysics *98*, 479 (1962).

[128] *S. Udenfriend, C. T. Clark, J. Axelrod*, and *B. B. Brodie*, J. biol. Chemistry *208*, 731 (1954).

[129] *H. Taniuchi* and *O. Hayaishi*, J. biol. Chemistry *238*, 283 (1963).

[130] *P. K. Ayengar, O. Hayaishi, M. Nakajima*, and *I. Tomida*, Biochim. biophysica Acta *33*, 111 (1959).

[131] *H. S. Posner, C. Mitoma, S. Rothberg*, and *S. Udenfriend*, Arch. Biochem. Biophysics *94*, 280 (1961).

[132] *H. Blaschko* and *W. G. Levine*, Brit. J. Pharmacol. Chemotherapy *15*, 625 (1960).

[133] *C. C. Porter, D. C. Titus, B. E. Sanders*, and *Eve Smith*, Science (Washington) *126*, 1014 (1957).

[134] *L. J. Weber* and *A. Horita*, Life Science *2*, 44 (1963).

[135] *E. Walaas* and *O. Walaas*, Arch. Biochem. Biophysics *95*, 151 (1961).

[136] *D. E. Green* and *D. E. Richter*, Biochem. J. *31*, 596 (1937).

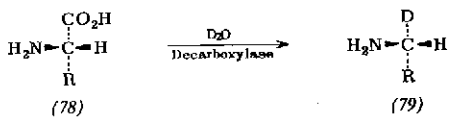
[137] *E. Walaas, O. Walaas, S. Haavaldsen*, and *B. Pedersen*, Arch. Biochem. Biophysics *100*, 97 (1963).

oxidase from salivary glands converts catecholamines into aminochromes [138], which react with hydrazines to form extractable and assayable derivatives.

2. Decarboxylases

An enzyme purified from the soluble fraction of guinea pig kidney decarboxylates a variety of amino acids. This enzyme has been named aromatic L-amino-acid decarboxylase [58]. The cofactor of this enzyme is pyridoxal phosphate whose reactive aldehyde group may condense with amines, such as norepinephrine [139], to form tetrahydroisoquinoline derivatives [140]. This side reaction may cause difficulties in the enzymatic assay of dopa. The enzyme also decarboxylates its own competitive inhibitors, namely α-methyl-α-amino acids, which are inhibitors of the enzyme both *in vitro* and *in vivo* [141]. An enzyme purified from rat liver is claimed to be unable to decarboxylate *p*-tyrosine, histidine, and tryptophan [142], but this result may be due to inadequate assay methods. Spectrofluorimetry is the method of choice [143]. *N*-Acetyl-5-hydroxytryptophan, 5-alkoxytryptophans [144], and 5- or 6-methyltryptophan [143] are not decarboxylated.

The decarboxylation of tyrosine *(78)* to form tyramine *(79)* in heavy water proceeds with retention of configuration [145].



(78) *(79)*

Numerous inhibitors of decarboxylation have been described [146], including the α-methyl-α-amino acids. The hydrazino analogue of α-methyldopa is an effective inhibitor but does not readily cross the blood-brain barrier [147] and is itself a substrate for the decarboxylase [148].

The specific histidine decarboxylase of mast cells [109] also requires pyridoxal phosphate as a cofactor [149]. It is not inhibited by α-methyl-α-amino acids, although at high concentrations α-methylhistidine does inhibit this enzyme specifically [150, 151]. Certain benzyloxyamines and benzylhydrazines are potent inhibitors of both enzymes [151–154].

3. Catechol O-Methyl Transferase (COMT)

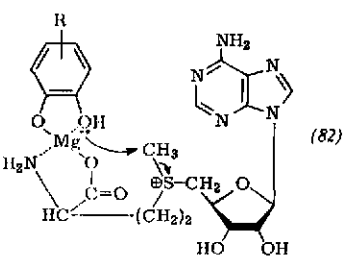
Since the isolation of this enzyme [155], which requires Mg^{2+} and *S*-adenosylmethionine as cofactors and which methylates only compounds containing a catechol moiety, its major rôle in the metabolism of catecholamines has become firmly established [1]. The enzyme normally methylates preferentially the *m*-hydroxy group with respect to the side-chain, except in the case of electron-withdrawing substituents (carbonyl) where *para*-methylation increases at the expense of *meta* [14]. *p-O*-Methylation of catecholamines occurs *in vitro* [14, 55] but as yet has not been demonstrated *in vivo* except for adrenalone and arterenone [55]. A sterically hindered catechol, such as 5-t-butyl-3,4-dihydroxyacetophenone *(80)* forms exclusively the 3-*O*-methyl derivative *(81)* [156].

(80) *(81)*

COMT = Catechol-O-methyltransferase

Pyrogallol and its derivatives are enzymatically methylated to a number of *O*-methyl derivatives [157–159]. The 2-hydroxy group of pyrogallol derivatives is usually, but not always preferentially methylated.

Further studies on COMT have substantiated the early formulation [14] of the substrate-*S*-adenosylmethionine-enzyme-magnesium complex *(82)* [160]. Formula *(82)*



(82)

[138] *J. Axelrod*, Fed. Proc. *22*, 388 (1963).

[139] *J. A. Buzard* and *P. D. Nytch*, J. biol. Chemistry *234*, 884 (1959).

[140] *H. F. Schott* and *W. G. Clark*, J. biol. Chemistry *196*, 449 (1952).

[141] *J. A. Oates, L. Gillespie, S. Udenfriend*, and *A. Sjoerdsma*, Science (Washington) *131*, 1890 (1960).

[142] *J. Awapara, R. P. Sandman*, and *C. Hanly*, Arch. Biochem. Biophysics *98*, 520 (1962).

[143] *W. Lovenberg, H. Weissbach*, and *S. Udenfriend*, J. biol. Chemistry *237*, 89 (1962).

[144] *V. Erspamer* and *M. B. Nobili*, Arch. int. Pharmacodynam. Thérap. *139*, 433 (1962); *V. Erspamer, V. Glässner, C. Pasini*, and *G. Stoppani*, Nature (London) *189*, 483 (1961).

[145] *B. Belleau* and *J. Burba*, J. Amer. chem. Soc. *82*, 5751 (1960).

[146] *W. G. Clark*, Pharmacol. Rev. *11*, 330 (1959).

[147] *C. C. Porter, L. S. Watson, D. C. Titus, J. A. Totaro*, and *S. S. Byer*, Biochem. Pharmacol. *11*, 1067 (1962).

[148] *S. Udenfriend, R. Connamacher*, and *S. M. Hess*, Biochem. Pharmacol. *8*, 419 (1961).

[149] *P. Hagen, N. Weiner, S. Ono*, and *F. L. Lee*, J. Pharmacol. exp. Therapeut. *130*, 9 (1960).

[150] *D. Mackay* and *D. M. Shepherd*, Biochim. biophysica Acta *59*, 553 (1962).

[151] *J. D. Reid* and *D. M. Shepherd*, Life Science *2*, 5 (1963).

[152] *D. J. Drain, M. Horlington, R. Lazare*, and *G. A. Poulter*, Life Science *1*, 93 (1962).

[153] *B. B. Brodie, R. Kuntzman, C. W. Hirsch*, and *E. Costa*, Life Science *1*, 81 (1962).

[154] *W. P. Burkard, K. F. Gey*, and *A. Pletscher*, Experientia *18*, 411 (1962).

[155] *J. Axelrod* and *R. Tomchick*, J. biol. Chemistry *332*, 702 (1958).

[156] *T. Matsuura, A. Nichinaga*, and *H. J. Cahnmann*, J. org. Chemistry *27*, 3620 (1962).

[157] *S. Archer, A. Arnold, R. K. Kullnig*, and *D. W. Wylie*, Arch. Biochem. Biophysics *87*, 153 (1960).

[158] *A. N. Booth* and *F. DeEds*, Biochim. biophysica Acta *65*, 495 (1962).

[159] *J. W. Daly, J. Axelrod*, and *B. Witkop*, Ann. New York Acad. Sci. *96*, 37 (1961).

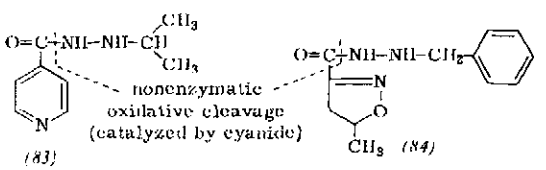
[160] *S. Senoh, Y. Tokuyama*, and *B. Witkop*, J. Amer. chem. Soc. *84*, 1719 (1962).

gives a suitable explanation for the present data on the position of methylation. The assumption of a 1:1:1 complex has received support from studies on the rôle of cations in COMT methylations [160] and from the nature of the non-competitive inhibition of COMT with tropolone, which has been shown to involve a 1:1 ratio of metal to inhibitor [161].

Because of the importance of COMT in the inactivation of catecholamines, many attempts have been made to find inhibitors [162–166] which *inter alia* would prolong the physiological half-life of (nor)epinephrine. Of these inhibitors, pyrogallol has been widely studied, in spite of its toxicity and instability. Other non-competitive inhibitors of COMT of lesser toxicity and greater potency and stability are dihydroxyphenylacetamide [167] and the tropolones [168]. *O*-Methyl transferase is also inhibited by high levels of thyroxine [169] and 3,5-diiodo-4-hydroxybenzoic acid [170]. Catechol intermediates in alkaloid biosyntheses are *p*-*O*-methylated exclusively by a novel COMT from plants [170a].

4. Amine Oxidases

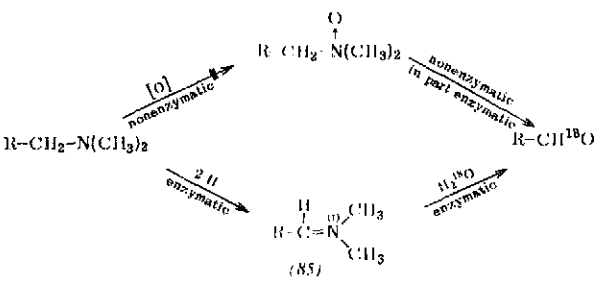
The enzyme MAO is intimately concerned with the metabolism of catecholamines which are oxidatively deaminated to the corresponding aldehydes. The final product is either an acid or an alcohol, depending on whether aldehyde oxidase or alcohol dehydrogenase supervenes. The enzyme is mitochondrial but has been solubilized [171]. Little is known of its cofactor requirements (flavine?) [172]. The inhibition of MAO with iproniazid *(83)* indicates two active enzymatic sites [173].



(83) *(84)*

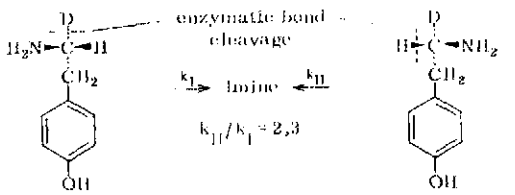
The inhibition involves first a non-enzymatic, non-hydrolytic, oxidative, cyanide-catalysed breakdown of iproniazid to isopropylhydrazine and acetone, followed by irreversible combination with the enzyme in a ratio of two moles of hydrazine to one mole of completely inhibited enzyme in analogy to the mode of action of isocarboxazid *(84)* [174]. The irreversible inhibition is not merely due to combination of the liberated hydrazines with a functional group at the active site of the enzyme. Pyruvate will prevent but not reverse inhibition [175]. Other carbonyl reagents such as semicarbazide do not cause inhibition, and the inhibition with hydrazines requires the presence of oxygen [176]. A study on the autooxidation of hydrazines catalysed by cupric ions indicates the formation of free radicals [177]. Such free radicals could combine irreversibly with the active sites of MAO after having been attracted and held there by other (non-covalent) binding forces.

The metabolism of tertiary amines such as *N*,*N*-dimethyltryptamine by MAO is of interest and led to an investigation of the rôle of *N*-oxides as intermediates [178]. It was found that oxygen in the resulting aldehyde was derived from $H_2{}^{18}O$, but not from $^{18}O_2$, so that no exchange of *N*-oxide with *N*,*N*-dimethyltryptamine occurred. Kinetic studies also contradicted the occurrence of an *N*-oxide as an intermediate, although the *N*-oxide did undergo slow oxidation, especially at low oxygen tensions. The enzymatic breakdown of a tertiary amine may go through the aldimmonium intermediate *(85)* which, being a "Decker base", is prone to hydrolysis [179].



(85)

Isotope studies on primary amines [180] favor imine formation *via* breaking of an α-C-H bond in the rate-determining step. With specifically deuterated tyramine



(86) R-α-Deutero-tyramine *(87)* S-α-Deutero-tyramine

[161] *J. V. Burba*, Ph. D. Thesis, University of Ottawa, Ottawa, Canada.

[162] *J. Axelrod* and *M. J. Laroche*, Science (Washington) *130*, 800 (1959).

[163] *J. Axelrod* and *R. Tomchick*, Nature (London) *184*, 2027 (1959).

[164] *Z. M. Bacq*, *L. Gosselin*, *A. Dresse*, and *J. Renson*, Science (Washington) *130*, 453 (1959).

[165] *S. Udenfriend*, *C. R. Creveling*, *M. Ozaki*, *J. W. Daly*, and *B. Witkop*, Arch. Biochem. Biophysics *84*, 249 (1959).

[166] *D. W. Wylie*, *S. Archer*, and *A. Arnold*, J. Pharmacol. exp. Therapeut. *130*, 239 (1960).

[167] *A. Carlsson*, *M. Lindqvist*, *S. Fila-Hromadko*, and *H. Corrodi*, Helv. chim. Acta *45*, 270 (1962).

[168] *B. Belleau* and *J. Burba*, Biochim. biophysica Acta *54*, 195 (1961).

[169] *A. D'Iorio* and *J. Leduc*, Arch. Biochem. Biophysics *87*, 224 (1960).

[170] *A. D'Iorio* and *C. Mavrides*, Canad. J. Biochem. Physiol. *40*, 1454 (1962).

[170a] *H. M. Fales*, *J. Mann*, and *S. H. Mudd*, J. Amer. chem. Soc. *85*, 2025 (1963).

[171] *H. Weissbach*, *B. G. Redfield*, and *S. Udenfriend*, J. biol. Chemistry *229*, 953 (1957).

[172] *A. N. Davison*, Physiol. Rev. *38*, 729 (1958).

[173] *T. E. Smith*, *H. Weissbach*, and *S. Udenfriend*, Biochemistry, in the press.

[174] *M. Schwartz*, J. Pharmacol. exp. Therapeut. *135*, 1 (1962).

[175] *A. Horita* and *C. Matsumoto*, Life Science *1*, 491 (1962).

[176] *B. M. Davison*, Biochem. J. *67*, 316 (1957).

[177] *L. E. Eberson* and *K. Persson*, J. med. pharmac. Chem. *5*, 738 (1962).

[178] *T. E. Smith*, *H. Weissbach*, and *S. Udenfriend*, Biochemistry *1*, 137 (1962).

[179] *D. Richter*, Biochem. J. *31*, 2022 (1937).

[180] *B. Belleau*, *M. Fang*, *J. Burba*, and *J. Moran*, J. Amer. chem. Soc. *82*, 5752 (1960).

(86) and *(87)*, prepared either by enzymatic decarboxylation of tyrosine or by asymmetric synthesis, MAO has been shown to exhibit stereospecificity [180] corresponding to that of alcohol dehydrogenase [181]. Deuterated tyramine and tryptamine show a direct correlation between the isotope effect on MAO oxidation and the prolonged *in vivo* activity. The physiological effect of [$^2H_2$]norepinephrine is not prolonged, as it would have been if inactivation by MAO had been the major pathway [182]. This is in keeping with observations on the effect of MAO inhibition on the action of phenethylamine, tyramine, norepinephrine, and epinephrine [183]. In deuterated kynuramine [184], bond cleavage of α- (and β-) hydrogen is important in the rate-determining transition state. Thus, the transition state should have an α-β carbon-carbon bond with partial double bond character. Since compounds of the phenylcyclopropylamine type have such a hybridized α-β bond, their efficacy as inhibitors of MAO [185] may well be due to their close resemblance to the transition state in MAO oxidation. Further analysis of the action of 2-phenylcyclopropylamines as inhibitors has shown that these reversible inhibitors do not compete with harmine (7-methoxy-1-methyl-9-pyrid[3,4-*b*]indole) for the same site or else combine with it in a non-competitive manner [186], whereas harmine and hydrazines do compete for the same site [187]. The family of MAO inhibitors [188] encompasses many types of compounds [189].

Assays of MAO activity *in vitro* have now been greatly simplified by the introduction of kynuramine as a substrate; its conversion into 4-hydroxyquinoline is accompanied by a loss of ultraviolet absorption at 360 mμ [190]. Extension of this method to dihydronorkynuramine leads to the formation of indigo [191], a reaction potentially useful for the development of a histochemical reagent for MAO, analogous to the use of a tetrazolium electron acceptor for studying the inhibition of MAO *in vitro* [192].

A sensitive assay of MAO activity permits direct measurement of MAO inhibition in man using jejunal mucosa [193]. An inherent fault of this method is the possibility of differential inhibition of various tissues by different inhibitors [194].

The inhibition of MAO by thiamine [195] is of interest, since nerves are reported to contain thiamine or a similar compound whose transport across the nerve membrane appears to be linked to nervous activity [196]. Hyperthyroid function causes a decrease in MAO levels and results in elevated levels of tryptamine and tyramine [197].

In addition to other amine oxidases, more than one monoamine oxidase [198] is present in mammals [199, 200]. There is also a diamine oxidase [200, 201], which is present in hog intestines and kidneys and oxidizes histamine, putrescine, and other diamines. This enzyme is inhibited by picolylamines [202]. Restoration of activity of diamine oxidase towards cadaverine but not towards histamine after inhibition by isonicotinylhydrazine can be accomplished by addition of ferricyanide. Semicarbazide or aminoguanidine inhibition is not reversed in this manner [203]. The enzyme probably requires pyridoxal phosphate as a cofactor [200].

Spermine oxidase and benzylamine oxidase occur in the plasma of many species [201, 204]. Spermine oxidase is crystalline and contains cupric ions and pyridoxal phosphate as prosthetic groups (4 Cu^{2+} and 2 pyridoxal phosphate per enzyme molecule). Two active sites have been postulated [205, 206]. Rabbit liver microsomes contain an enzyme which deaminates amphetamine [207]. An enzyme, histaminase, is specific for 1-methylhistamine and is different from diamine oxidase [207a].

5. Dopamine β-Oxidase (Norepinephrine Synthetase)

The enzyme which forms β-phenylethanolamines has been purified from chromaffin granules of the adrenal medulla. It requires ascorbic acid and fumaric acid as cofactors [208]. Without ascorbic acid, a catechol compound can serve as an alternative reducing agent [209]. The enzyme is non-specific and accepts a variety of substrates including phenethylamine [209], tyramine [210],

[181] *F. A. Loewus, F. H. Westheimer,* and *B. Vennesland,* J. Amer. chem. Soc. *75,* 5018 (1953).

[182] *B. Belleau, J. Burba, M. Pindell,* and *J. Reiffenstein,* Science (Washington) *133,* 102 (1961).

[183] *E. Griesemer, C. Barsky, C. A. Dragstedt, J. A. Wells,* and *E. A. Zeller,* Proc. Soc. exp. Biol. Med. *84,* 699 (1953).

[184] *B. Belleau* and *J. Moran,* J. med. pharmac. Chem. *5,* 215 (1962).

[185] *S. Sarkar, R. Banerjee, M. S. Ise,* and *E. A. Zeller,* Helv. chim. Acta *43,* 439 (1960).

[186] *C. L. Zinkle, C. Kaiser, D. H. Tedeschi, R. E. Tedeschi,* and *A. Burger,* J. med. pharmac. Chem. *5,* 1265 (1962).

[187] *A. Horita* and *W. R. McGrath,* Biochem. Pharmacol. *3,* 206 (1960).

[188] *E. A. Zeller,* Ann. New York Acad. Sci. *80,* 551 (1959).

[189] *M. Ozaki, H. Weissbach, A. Ozaki, B. Witkop,* and *S. Udenfriend,* J. med. pharmac. Chem. *2,* 591 (1960).

[190] *H. Weissbach, T. E. Smith, J. W. Daly, B. Witkop,* and *S. Udenfriend,* J. biol. Chemistry *235,* 1160 (1960).

[191] *Y. Kanaoka, H. Weissbach, T. E. Smith,* and *B. Witkop,* J. Amer. chem. Soc. *83,* 732 (1961).

[192] *K. K. Mustakallio* and *E. Levonen,* Science (Washington) *134,* 344 (1961).

[193] *R. J. Levine* and *A. Sjoerdsma,* Clin. Pharmacol. Therap. *5,* 22 (1963).

[194] *W. R. McGrath* and *A. Horita,* Toxicol. appl. Pharmacol. *4,* 178 (1962).

[195] *H. Y. Meltzer,* Biochem. Pharmacol. *7,* 277 (1961).

[196] *I. H. Heller, L. S. Wolfe,* and *S. Hesse,* J. Neurochemistry *9,* 443 (1962).

[197] *R. J. Levine, J. A. Oates, A. Vendsalu,* and *A. Sjoerdsma,* J. clin. Endocrinol. Metabolism *22,* 1242 (1962).

[198] *W. Hardegg* and *E. Heilbronn,* Biochim. biophysica Acta *51,* 553 (1961).

[199] *H. Blaschko,* Pharmacol. Rev. *4,* 415 (1952).

[200] *H. Blaschko,* Brit. med. Bull. *9,* 146 (1953).

[201] *H. Blaschko,* J. Physiology *145,* 384 (1959).

[202] *H. Blaschko* and *S. Kurzepa,* Brit. J. Pharmacol. Chemotherapy *19,* 544 (1962).

[203] *Y. Kobayashi* and *T. Okuyama,* Biochem. Pharmacology *11,* 949 (1962).

[204] *H. Blaschko* and *R. Bonney,* Proc. Roy. Soc. (London) Ser. B, *156,* 268 (1962).

[205] *H. Yamada* and *K. T. Yasunobu,* J. biol. Chemistry *237,* 1511 and 3077 (1962).

[206] *H. Yamada* and *K. T. Yasunobu,* Biochem. biophys. Res. Commun. *8,* 387 (1962).

[207] *J. Axelrod,* J. biol. Chemistry *214,* 753 (1955).

[207a] *R. Kappeller-Adler* and *H. Macfarlane,* Biochim. biophysica Acta *67,* 542 (1963).

[208] *E. Y. Levin, B. Levenberg,* and *S. Kaufman,* J. biol. Chemistry *235,* 2080 (1960).

[209] *E. Y. Levin* and *S. Kaufman,* J. biol. Chemistry *236,* 2043 (1961).

[210] *J. J. Pisano, C. R. Creveling,* and *S. Udenfriend,* Biochim. biophysica Acta *43,* 566 (1960).

epinine [211,212], and a variety of other amines (3-methoxytyramine, α-methyltyramine, *m*-tyramine, α-methyldopamine, mescaline, *etc.*) [34,213,214]. Its ability to hydroxylate the non-phenolic compound phenethylamine makes the postulation of quinone or quinone methine intermediates superfluous. The hydroxyl oxygen is derived from $^{18}O_2$, not $H_2{}^{18}O$ [122]. In the conversion of tyramine into octopamine, the β-hydroxy group underwent solvent exchange during purification and the results were thus not definitive [215]. [β,β-$^3H_2$]Dopamine loses only one β-hydrogen in the process of enzymatic hydroxylation to norepinephrine [8]. No loss of α-hydrogens occurs [216]. Thus the oxidation appears to involve direct stereospecific attack of an oxygen moiety on one β-hydrogen.

The lack of substrate-specificity of the enzyme has led to a search for inhibitors, including those isosteric with known substrates [34,217,218]. Benzylhydrazines and benzyloxyamines are extremely active competitive inhibitors [34,217]. Their *m*-hydroxy derivatives inhibit the formation of brain norepinephrine while leaving dopamine and serotonin levels unaffected [219]. Anaerobic or aerobic preincubation of these inhibitors with the enzyme leads to non-competitive inhibition, although the enzyme activity can be regenerated by prolonged dialysis [220]. The enzyme is difficult to inhibit *in vivo* [219,221], and the duration of action of the compounds tested is short. Adrenalone inhibits the synthesis of norepinephrine from dopamine *in vitro* [218] and *in vivo* [222].

6. N-Methylases and N-Acetylases

N-Methylation and *N*-acetylation of amines has been known for many years but only recently have the enzymes involved been partially purified and studied.

Phenethanolamine *N*-methyl transferase has been purified from the soluble fraction of adrenal medulla [223]. With *S*-adenosylmethionine as a cofactor, it specifically methylates β-phenylethanolamines; phenethylamines do not serve as substrates.

A non-specific *N*-methylase from the soluble fraction of rabbit lung with *S*-adenosylmethionine as a cofactor methylates a variety of endogenous amines, such as catecholamines, serotonin, tyramine, tryptamine, and histamine, and exogenous amines, such as mescaline and normorphine [91].

Amines are also acetylated by an enzyme isolated from the soluble fraction of rat liver [18].

IV. Distribution and Localization of Amines and Enzymes

In the preceding sections, an attempt has been made to indicate the localization, both with regard to tissues and cells, of enzymes concerned with amine biosynthesis and metabolism. The preliminary and summary Chart 8 presents a picture of the localization of amines and enzymes in the central nervous system [224–237].

The formation of amines from [2-^{14}C]tyrosine in cat brain slices has been investigated. The caudate nucleus, a region normally high in dopamine, synthetized large amounts of this amine, while other regions gave rise to small amounts of only dopamine and norepinephrine [238].

The distribution of amino acids, amines, and oxidation products in different parts of rabbit brain after administration of [2-^{14}C]dopa follows a characteristic pattern. As expected, metabolism occurs slowly in the cerebrum and cerebellum, but decarboxylation proceeds rapidly in the caudate nucleus and the diencephalon (hypothalamus and thalamus) and mesencephalon (mid-brain). In the caudate nucleus, the amine levels remain high; in the diencephalon and mesencephalon, the concentrations of oxidation products exceed the amine levels [239]. A similar study exists on the production of 5-hydroxyindole-3-acetic acid after administration of 5-hydroxytryptophan [240].

In addition to the topography of amines and enzymes in the brain, the subcellular distribution of catecholamines and serotonin is of interest. This question is being investigated with the help of density gradient centrifugations, radioautography, and electron microscopy.

[211] *W. F. Bridgers* and *S. Kaufman*, J. biol. Chemistry *237*, 526 (1962).

[212] *M. Goldstein* and *J. F. Contrera*, Biochem. Pharmacology *7*, 77 (1961).

[213] *M. Goldstein* and *J. F. Contrera*, J. biol. Chemistry *237*, 1898 (1962).

[214] *M. Goldstein* and *J. F. Contrera*, Experientia *17*, 447 (1961).

[215] *C. R. Creveling*, Ph. D. Thesis, Georgetown University, Washington, D.C., 1962.

[216] *W. J. Smith* and *N. Kirshner*, J. biol. Chemistry *237*, 1890 (1962).

[217] *C. R. Creveling, J. B. van der Schoot*, and *S. Udenfriend*, Biochem. biophys. Res. Commun. *8*, 215 (1962).

[218] *M. Goldstein* and *J. F. Contrera*, Experientia *18*, 334 (1962).

[219] *R. Kuntzman, E. Costa, C. R. Creveling, C. W. Hirsch*, and *B. B. Brodie*, Life Science *1*, 85 (1962).

[220] *J. B. van der Schoot, C. R. Creveling, T. Nagatsu*, and *S. Udenfriend*, J. Pharmacol. exp. Therapeut., in the press.

[221] *B. Nikodijevic, C. R. Creveling*, and *S. Udenfriend*, J. Pharmacol. exp. Therapeut. *140*, 224 (1963).

[222] *M. Goldstein, J. M. Musacchio, M. C. Kenin, J. F. Contrera*, and *M. D. Rice*, Biochem. Pharmacology *11*, 809 (1962).

[223] *J. Axelrod*, J. biol. Chemistry *237*, 1657 (1962).

[224] *A. Carlson*, Pharmacol. Rev. *11*, 490 (1959).

[225] *T. L. Sourkes*, Ann. New York Acad. Sci. *66*, 187 (1957).

[226] *J. Axelrod, W. Albers*, and *C. D. Clemente*, J. Neurochemistry *4*, 68 (1959).

[227] *S. Udenfriend* and *C. R. Creveling*, J. Neurochemistry *4*, 350 (1959).

[228] *A. Bertler* and *E. Rosengren*, Acta physiol. scand. *47*, 350 (1959).

[229] *R. Kuntzman, P. A. Shore, D. Bogdanski*, and *B. B. Brodie*, J. Neurochemistry *6*, 226 (1961).

[230] *D. F. Bogdanski, H. Weissbach*, and *S. Udenfriend*, J. Neurochemistry *1*, 272 (1957).

[231] *A. Bertler*, Acta physiol. scand. *51*, 97 (1961).

[232] *G. R. Pschoidt* and *H. E. Himwich*, Biochem. Pharmacology *12*, 65 (1963).

[233] *W. D. M. Paton*, Ann. Rev. Physiol. *20*, 431 (1958).

[234] *J. Crossland*, J. Pharmacy Pharmacol. *12*, 1 (1960).

[235] *S. Udenfriend* and *D. F. Bogdanski*, J. Pharmacol. exp. Therapeut. *116*, 7 (1956).

[236] *C. F. Baxter, E. Roberts*, and *E. Eidelberg*, Fed. Proc. *18*, 187 (1959).

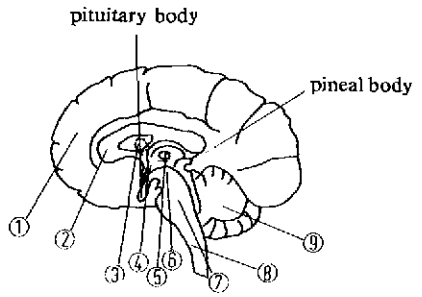
[237] *K. A. C. Elliott* and *H. H. Jasper*, Physiol. Rev. *39*, 383 (1959).

[238] *D. T. Masuoka, H. F. Schoff*, and *L. Petriello*, J. Pharmacol. exp. Therapeut. *139*, 73 (1963).

[239] *A. Pletscher* and *K. F. Gey*, Experientia *18*, 512 (1962).

[240] *B. E. Roos*, Life Science *1*, 25 (1962).

Serotonin, acetylcholine [241–245], and norepinephrine [246] have been shown to occur in brain particles corresponding to nerve endings. The same density gradient technique has been applied to norepinephrine and other amines in heart and adrenals [246]. Radioautograms



have helped to localize norepinephrine in various tissues [246] and to define the structure of sympathetic nerve endings [247,248]. Electron microscopy has shed some light on the mode of release of catecholamines from adrenal medulla granules. The granules apparently discharge discrete quanta of about 8 million molecules of epinephrine [249,250].

Another tool for the study of the more subtle metabolic aspects of norepinephrine and other amines is the spectrofluorimetric assay [251–253] of their condensation products with formaldehyde. This approach permits histochemical differentiation between primary or secondary catecholamines and serotonin.

V. Interactions of Drugs and Amines

The interactions of drugs with endogenous amines and with the enzymes that synthetize, inactivate, and degrade them is quite complex and has been the subject of numerous reviews [254–257].

The mode of action of a particular drug may depend on blocking of the active transport of an amine or its precursor, on inhibition of a crucial enzyme, or on competition for storage

	1 Cerebrum	2 Corpus callosum	3 Caudate nucleus (basal ganglion)	4 Hypothalamus	5 Thalamus	6 Mid-brain	7 Pons	8 Medulla	9 Cerebellum
Amines [224,225,229,231–234, 236,237]									
Dopamine [a]	trace	trace	++++	++	+	+	trace	trace	trace
Norepinephrine	trace	trace	+	+++	++	++	++	++	trace
Serotonin	trace	trace	++	++++	++	++	+	trace	trace
Histamine	trace		trace	+++	trace			trace	trace
Acetylcholine	+++	+++	++++	+++	++++	+++		+++	trace
γ-Aminobutyric acid [b]	200	50		400		300–500	250	200	200
Enzymes [c] [172,226–230,235]									
Decarboxylase (dopa)	20	30	420	200	130	220	100	70	10
Dopamine β-oxidase (dopamine)	trace		0.8	1.1					trace
COMT (epinephrine)	80	100	100	90		110	1	9	40
MAO (serotonin)	800	400	900	1600	900	800	900	1100	900
Function of brain area	Conciousness, speech association, motor and sensory relays	Nerve fibres between hemispheres	Integration of motor activity	Emotions	Sensation (pain, pleasure)	Motor activity of certain types	Sensory, motor nerves	Sensory, motor nerves	Muscle coordination and body equilibrium

Chart 8. Brain topography of endogenous amines and enzymes.

[a] Trace = 0–0.15 μg/g of tissue; + = 0.15–0.30; ++ = 0.30–0.60; +++ = 0.60–1.5; ++++ = 1.5–15.
[b] μg/ml.
[c] Enzyme activity in μg of substrate per g of tissue per hour.
Substrates in parentheses.

[241] *R. W. Ryall*, Biochem. Pharmacology *11*, 1234 (1962).

[242] *I. A. Michaelson* and *V. P. Whittaker*, Biochem. Pharmacology *11*, 505 (1962).

[243] *R. W. Ryall*, Nature (London) *196*, 680 (1962).

[244] *V. P. Whittaker*, Nature (London) *195*, 1100 (1962).

[245] *I. A. Michaelson* and *V. P. Whittaker*, Biochem. Pharmacology *12*, 203 (1963).

[246] *L. T. Potter* and *J. Axelrod*, Nature (London) *194*, 581 (1962); *D. E. Wolfe, L. T. Potter, K. C. Richardson*, and *J. Axelrod*, Science (Washington) *138*, 440 (1962).

[247] *T. Samorajski* and *B. H. Marks*, J. Histochem. Cytochem. *10*, 392 (1962).

[248] *B. H. Marks, T. Samorajski*, and *E. J. Webster*, J. Pharmacol. exp. Therapeut. *138*, 376 (1962).

[249] *E. D. P. De Robertis* and *D. D. Sabatini*, Fed. Proc. *19*, 70 (1959).

[250] *W. R. Burack, E. Avery, P. R. Draskóczy*, and *N. Weiner*, Biochem. Pharmacology *9*, 85 (1962).

[251] *A. Carlsson, B. Falck*, and *N.-Å. Hillarp*, Acta physiol. scand. *54*, 385 (1962).

[252] *A. Carlsson, B. Falck*, and *N.-Å. Hillarp*, Acta physiol. scand. *56*, Suppl. 196 (1962).

[253] *B. Falck*, Acta physiol. scand. *56*, Suppl. 197 (1962).

[254] *W. S. Peart*, Ann. Rev. Pharmacol. *2*, 251 (1962).

[255] *B. B. Brodie* and *E. Costa* in: Monamines et Systeme Nerveux Central. Georg & Cie, S. A., Geneva, Switzerland, 1962.

[256] *P. A. Shore*, Pharmacol. Rev. *14*, 531 (1962).

[257] *J. Axelrod* in: Proc. Symp. on Clin. Chem. of Monoamines. Elsevier, Amsterdam, in the press.

sites or receptors. The endogenous compounds with which the drug competes have a special affinity for selected sites on proteins. Drugs generally act at all of these selected sites to different degrees. *In vitro* effects will be modified *in vivo* by competing reactions for the drug molecule and by the ability of the drug to reach its target protein. All of these factors must be considered in assessments of drug amine interactions.

Chart 9 emphasizes the diversity of action of various drugs. Many effects have been found in one simple system only and not in another or in a more integrated system. Again, many of the compounds have been incompletely studied, or only with regard to certain selected effects. Moreover, drugs which interfere with release do

The action of sympathomimetic amines for which the terms "indirect", "direct", or "mixed" have been used [259] is related either to their ability to act directly on the receptor (*e.g.* with aramine and neosynephrin) or their ability to release bound norepinephrine (*e.g.* with tyramine, phenethylamine, and amphetamine). "Mixed" amines, such as ephedrine, have actions comprising both effects [260,261].

Of interest in this regard is D-(−)-pseudoephedrine, which augments the response to norepinephrine but blocks the pressor response to D-(−)-ephedrine [262]. Thus, the re-

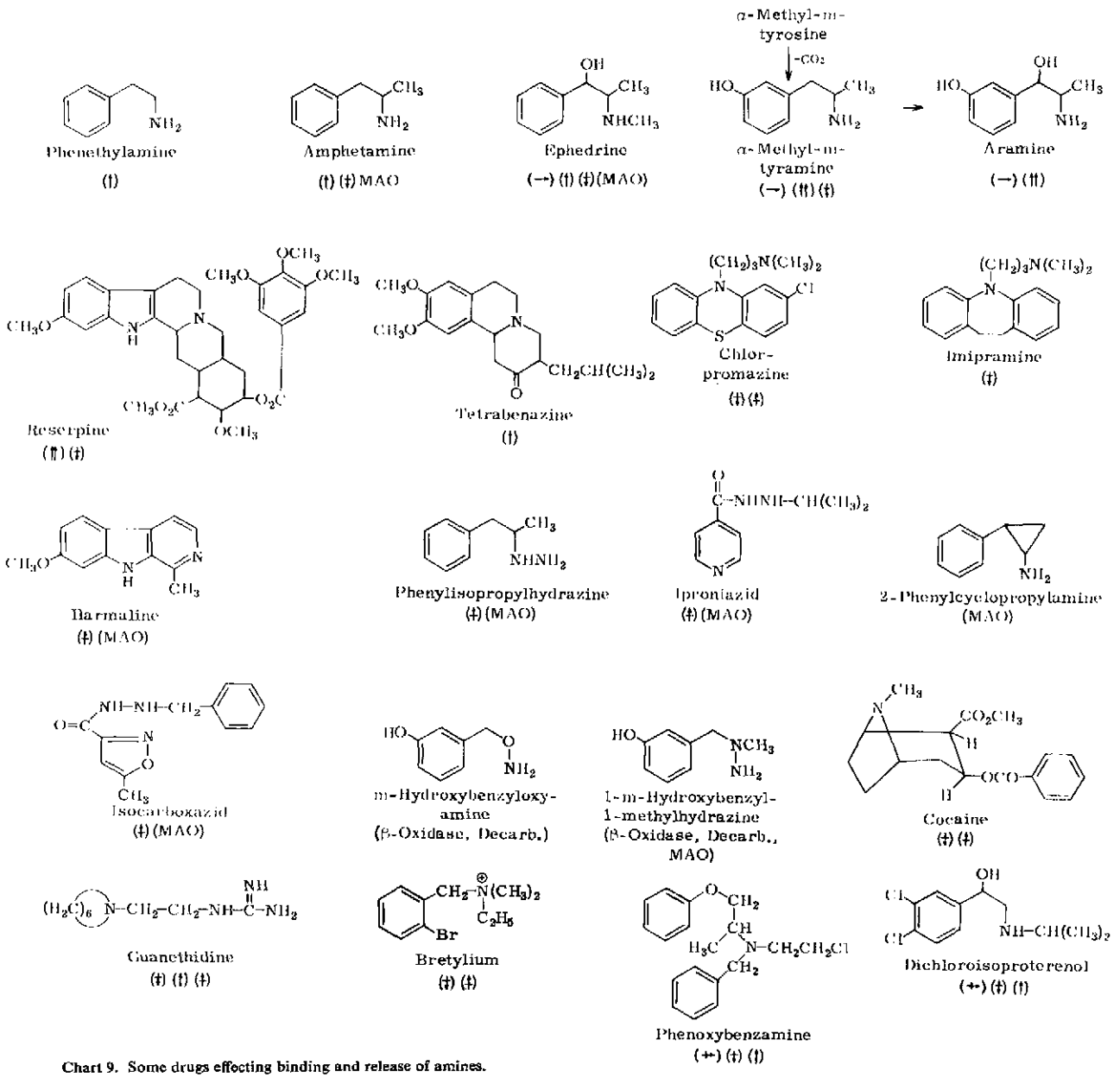


Chart 9. Some drugs effecting binding and release of amines.

(↑): Releases (↕): Blocks release (↕): Blocks uptake (→): Sympathomimetic (↔): Sympatholytic MAO, decarb., β-oxidase: Compound inhibits monoamine oxidase, decarboxylase or dopamine β-oxidase

so by different mechanisms. For example, chlorpromazine and MAO inhibitors appear to antagonize only drug-induced release [256,257], while blocking or release by guanethidine and bretylium may reflect on the cholinergic aspects of adrenergic nerves [256,258].

[258] *J. H. Burn* and *M. J. Rand*, Advances Pharmacology *1*, 30 (1962).

[259] *J. H. Burn* and *M. J. Rand*, J. Physiology *144*, 314 (1953).

[260] *U. Trendelenburg, A. Muskus, W. W. Fleming*, and *B. Gomez Alonso de la Sierra*, J. Pharmacol. exp. Therapeut. *138*, 170 (1962).

[261] *J. L. Schmidt* and *W. W. Fleming*, J. Pharmacol. exp. Therapeut. *139*, 230 (1963).

[262] *J. B. LaPidus, A. Tye, P. Patil*, and *B. Z. Modi*, J. med. Chemistry *6*, 76 (1963).

leasing action of ephedrine seems to be blocked by its diastereoisomer which, however, causes no response alone.

The release of norepinephrine by amines, such as tyramine and phenethylamine, from medullary granules [263] results in a direct balance between displaced norepinephrine and replacing amine. This is in contrast to the potent releasing action of aramine, whose potency rivals that of reserpine [264].

Some of the amines interfere with uptake [256,265]. Amphetamine and ephedrine are also weak MAO inhibitors [266].

Reserpine is the classical example of a releasing agent for catecholamines and serotonin [256]; however, at low concentrations in bovine splenic nerves it inhibits release of amines including tyramine-induced release [267]. In adrenal granules, reserpine interferes with uptake of dopamine but not with its subsequent conversion into norepinephrine [268]. In contrast, studies of brain revealed no concentration of dopamine, not even in the caudate nucleus [269].

The dual pathway of inactivation of norepinephrine by MAO, on the one hand, and by COMT, on the other, has been studied in heart. The mode of release of bound norepinephrine can be classified as either intracellular release leading to metabolism by MAO or extracellular release of active amine which is then metabolized by COMT. Nervous stimulation [270], tyramine [39,271], acetylcholine, and 1,1-dimethyl-4-phenylpiperazinium salts [272] cause extracellular release. Reserpine, which releases large amounts of amine, does so intracellularly, thus leading to metabolism by MAO [271]. Treatment with a MAO-inhibitor does not cause release but influences reserpine-induced release, since the amine must then diffuse out of the cell and then undergo inactivation by COMT. Guanethidine and α-methyldopa cause mainly intracellular release, but α-methyldopa also inhibits COMT in addition [272]. Whether similar mechanisms apply in the brain is unknown. In heart slices, norepinephrine is metabolized by COMT but in brain slices by MAO [269].

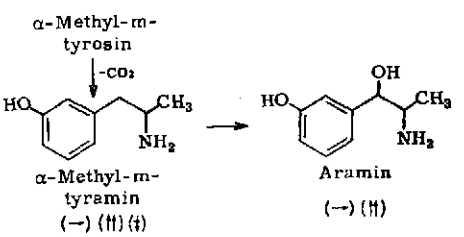
Tetrabenazine, like reserpine, causes release of serotonin and catecholamines in brain and, together with other benzoquinolizines, is the subject of a recent review [273].

Chlorpromazine blocks uptake [274], antagonizes reserpine-induced release of catecholamines [275], and counteracts the rise in brain serotonin induced by MAO inhibitors [275,276]. Imipramine or its active metabolite demethylimipramine [277] is an antidepressant which counteracts reserpine-induced depression [278] and has similar biochemical properties and therefore inhibits catecholamine uptake [274]. Imipramine differs from chlorpromazine in that it increases the metabolism of serotonin presumably by interfering with uptake, while chlorpromazine has no effect [105].

MAO inhibitors such as harmaline, phenylcyclopropylamines, phenylisopropylhydrazine, and iproniazid have the effect of blocking amine release and antagonizing the releasing action of reserpine and guanethidine [256, 279].

Decarboxylase inhibitors also act by various mechanisms. α-Methyldopa and α-methyl-*m*-tyrosine are potent inhibitors of the decarboxylating enzyme and decrease the levels of serotonin, dopamine, and norepinephrine. The levels of serotonin and dopamine soon return to normal, whereas norepinephrine levels remain low for long periods [280–282]. It has now been shown that decarboxylation of the inhibitor occurs *in vivo* and that the resulting α-methyl-*m*-tyramine is responsible for the long-term norepinephrine depletion [264,283,284].

α-Methyldopamine and *O*-methylated and deaminated products result similarly from α-methyldopa [285]. β-Hydroxylation of the amine formed by decarboxylation of α-methyl-*m*-tyrosine [286] *in vivo* leads to the very potent releasing agent aramine [264]. The presence of



[263] *H. J. Schümann* and *A. Philippa*, Int. J. Neuropharmacology *1*, 179 (1962).

[264] *S. Udenfriend* and *P. Zaltzman-Nirenberg*, J. Pharmacol. exp. Therapeut. *138*, 194 (1962).

[265] *S. M. Hess*, Arch. int. Pharmacodynam. Thérap. *138*, 584 (1962).

[266] *P. J. G. Mann* and *J. H. Quastel*, Biochem. J. *34*, 414 (1960).

[267] *U. S. von Euler* and *F. Lishajko*, Biochem. Pharmacology *9*, 77 (1962).

[268] *N. Kirshner*, J. biol. Chemistry *237*, 2311 (1962).

[269] *H. J. Dengler, I. A. Michaelson, H. E. Spiegel*, and *E. Titus*, Int. J. Neuropharmacology *1*, 23 (1962).

[270] *G. Hertting* and *J. Axelrod*, Nature (London) *192*, 161 (1961).

[271] *I. J. Kopin* and *E. K. Gordon*, J. Pharmacol. exp. Therapeut. *138*, 351 (1962).

[272] *I. J. Kopin* and *E. K. Gordon*, J. Pharmacol. exp. Therapeut. *140*, 209 (1963).

[273] *A. Pletscher, A. Brossi*, and *K. F. Gey*, Int. Rev. Neurobiol. *6*, 275 (1962).

[274] *G. Hertting, J. Axelrod*, and *R. W. Patrick*, Biochem. Pharmacology *8*, 246 (1961).

[275] *K. F. Gey* and *A. Pletscher*, Ann. New York Acad. Sci. *66*, 271 (1957).

[276] *C. Morpurge*, Biochem. Pharmacology *11*, 967 (1962).

[277] *L. Meduna, L. G. Abood*, and *J. H. Biel*, J. Neuropsychiat. *2*, 232 (1961).

[278] *M. S. Kline, G. Simpson*, and *B. B. Brodie*, Int. J. Neuropharmacology *1*, 55 (1962).

[279] *J. Axelrod, G. Hertting*, and *R. W. Patrick*, J. Pharmacol. exp. Therapeut. *134*, 325 (1961).

[280] *S. M. Hess, R. H. Connamacher, M. Ozaki*, and *S. Udenfriend*, J. Pharmacol. exp. Therapeut. *134*, 129 (1961).

[281] *C. C. Porter, J. A. Totaro*, and *C. M. Leiby*, J. Pharmacol. exp. Therapeut. *134*, 139 (1961).

[282] *E. Costa, G. L. Gessa, R. Kuntzman, C. W. Hirsch*, and *B. B. Brodie*, Ann. New York Acad. Sci. *96*, 118 (1962).

[283] *T. L. Sourkes, G. F. Murphy*, and *B. Chavez-Lara*, J. med. pharmac. Chem. *5*, 204 (1962).

[284] *G. L. Gessa, E. Costa, R. Kuntzman*, and *B. B. Brodie*, Life Science *1*, 353 (1962).

[285] *C. C. Porter* and *D. C. Titus*, J. Pharmacol. exp. Therapeut. *139*, 77 (1963).

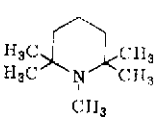
[286] *A. Carlsson* and *M. Lindqvist*, Acta physiol. scand. *54*, 87 (1962).

α-methyl-*m*-tyramine and aramine in brain tissues during prolonged depletion of norepinephrine is still a matter of controversy. *Carlsson* [287] found high levels after seven days, while other workers, using a different isolation procedure, observed a rapid disappearance of decarboxylation products [264,284].

m-Hydroxybenzyloxyamines and -hydrazines are effective inhibitors of decarboxylases [131–133] and β-oxidase [34,217,219]; the hydrazines also inhibit MAO [152,153].

Cocaine sensitizes nerve preparations to norepinephrine by interference with uptake [274] and antagonizes the action of tyramine [288], probably by interfering with its uptake and thus causing some inhibition of the release of norepinephrine [289–291].

Both guanethidine and bretylium appear to inhibit the release of norepinephrine onto receptors. Guanethidine has another long-term effect, *viz.* it depletes norepinephrine stores [256,292–294]. Both drugs inhibit the uptake of norepinephrine and antagonize reserpine-induced release [295]. Other ganglionic blocking agents, *e.g.* pempidine *(88)* or chlorisondamine *(89)*, inhibit both spontaneous and reserpine-induced release of norepinephrine [296]. Attempts to correlate storage sites and receptor sites have shown that certain blocking agents, *e.g.* phentolamine *(90)*, benzodioxane *(91)*, and dibenamine *(92)* also release norepinephrine from granules



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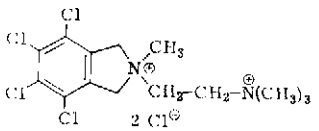
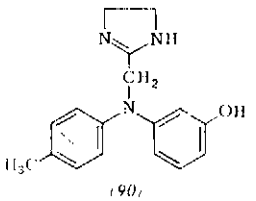


(89) (±)

[297], while others, *e.g.* phenoxybenzamine [274] and dichloroisoproterenol [298], inhibit norepinephrine uptake. COMT inhibitors, *e.g.* pyrogallol, potentiate the response to exogenous catecholamines [166,299,300] including isoproterenol [301], which is *O*-methylated *in vivo* [51]. Although pyrogallol normally does not change heart and brain levels of catecholamines in contrast to



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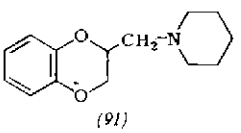

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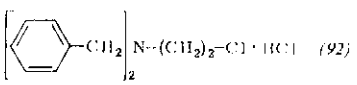


(92)

elevated brain levels with MAO inhibitors [302], intracisternal injections of pyrogallol result in a marked increase in brain catecholamines; this suggests that pyrogallol possibly cannot pass the blood-brain barrier readily [303]. The use of COMT inhibitors such as dihydroxyphenylacetamide [167] or tropolone derivatives [168] might overcome this problem. However, dihydroxyphenylacetamide has an inhibitory effect on the synthesis of serotonin and catecholamines in brain which may be related to inhibition of hydroxylating enzymes [287,303a].

Many of the drugs discussed also influence the uptake, storage, and release of serotonin [233]. Tyramine, amphetamine, guanethidine, cocaine, and chlorpromazine have little effect on infused serotonin, while tryptamine, reserpine, and imipramine decrease tissue storage and increase metabolism [105], presumably either by release or by interference with uptake. MAO inhibitors increase the tissue levels of serotonin and slow down its rate of destruction [105]. Similar interference with the central metabolism of tryptamine by inhibition of MAO leads to psychotic effects [304]. The depressant action of reserpine may be due to impaired storage of serotonin, since lowering of the norepinephrine level with α-methyl-α-amino acids does not result in sedation [305]. Interestingly enough, the depression induced by reserpine is overcome by administration of dopa and, less effectively, of 5-hydroxytryptophan [306]. A correlation between "CNS-depressants and -stimulants" with free and bound serotonin in brain has been elaborated [307], and shows that the amount of free serotonin is greatly increased by depressant drugs; this effect is in keeping with the depressant action of serotonin on evoked potentials in many parts of the brain [308]. Antagonists of serotonin have been reviewed recently [309].

[287] *A. Carlsson*, unpublished results.

[288] *U. Trendelenburg, A. Muskus, W. W. Fleming*, and *B. Gomez Alonso de la Sierra*, J. Pharmacol. exp. Therapeut. *138*, 181 (1962).

[289] *G. Hertting, J. Axelrod*, and *R. W. Patrick*, Biochem. Pharmacology *8*, 246 (1961).

[290] *R. Lindmar* and *E. Muscholl*, Arch. exp. Pathol. Pharmakol. *242*, 214 (1961).

[291] *M. F. Lockett* and *K. E. Eakins*, J. Pharmacy Pharmacol. *12*, 513 (1960).

[292] *R. Kuntzman, E. Costa, G. L. Gessa*, and *B. B. Brodie*, Life Science *1*, 65 (1962).

[293] *R. Cass* and *T. L. B. Spriggs*, Brit. J. Pharmacol. Chemotherapy *17*, 442 (1961).

[294] *M. D. Day* and *M. J. Rand*, J. Pharmacy Pharmacol. *14*, 541 (1962).

[295] *G. Hertting, J. Axelrod*, and *R. W. Patrick*, Brit. J. Pharmacol. Chemotherapy *18*, 161 (1962).

[296] *G. Hertting, L. T. Potter*, and *J. Axelrod*, J. Pharmacol. exp. Therapeut. *136*, 289 (1962).

[297] *A. D'Iorio* and *J. G. Laguë*, Canad. J. Biochem. Physiol. *41*, 121 (1963).

[298] *H. J. Dengler, H. E. Spiegel*, and *E. O. Titus*, Nature (London) *191*, 816 (1961).

[299] *Z. M. Bacq*, Arch. int. Physiol. *42*, 340 (1936); *44*, 15 (1936).

[300] *M. Goffart*, Arch. int. Pharmacodynam. Thérap. *139*, 476 (1962).

[301] *H. Konzen*, Arch. int. Pharmacodynam. Thérap. *139*, 558 (1962).

[302] *J. R. Crout, C. R. Creveling*, and *S. Udenfriend*, J. Pharmacol. exp. Therapeut. *132*, 269 (1961).

[303] *M. Masami, Y. Hiroshi*, and *I. Reiji*, Biochem. Pharmacology *11*, 1109 (1962).

[303a] *B.-E. Ross* and *B. Werdinius*, Life Science *2*, 92 (1963).

[304] *J. A. Oates* and *A. Sjoerdsma*, Neurology *10*, 1076 (1960).

[305] *G. L. Gessa, E. Costa, R. Kuntzman*, and *B. B. Brodie*, Life Science *1*, 441 (1962).

[306] *A. Carlssen, M. Lindqvist*, and *T. Magnusson*, Nature (London) *180*, 1200 (1957).

[307] *M. J. Giarman* and *S. M. Shanberg*, Biochem. Pharmacology *9*, 93 (1962).

[308] *A. Pineda* and *R. S. Snider*, Neurology *13*, 166 (1963).

[309] *L. Gyermek*, Pharmacol. Rev. *13*, 399 (1961).

VI. Interplay of Endogenous Amines

Antagonism between various amines, *e.g.* between acetylcholine and (nor)epinephrine in rat uterus, or between acetylcholine and serotonin in mollusc heart [310], are well known phenomena. Norepinephrine, epinephrine, and histamine antagonize serotonin [311], and serotonin in turn may either antagonize or be synergistic to norepinephrine [312, 313]. The release of catecholamines by tyramine is well documented. Tryptamine releases serotonin [105], histamine releases catecholamines [314], and is itself released by epinephrine [315] and serotonin [316]. A metabolite of dopamine, 2,4,5-trihydroxyphenethylamine [8] is quite active as a releasing agent for norepinephrine in heart [317].

Centrally inhibitory amino acids and polypeptides, such as γ-aminobutyric acid [237] and substance P [318], must be mentioned in this connection, although their role in central activity in vertebrates is as yet unclear [319]. Metabolites of γ-aminobutyric acid are *inter alia* γ-aminobutyrylhistidine [320] and γ-guanidinobutyric acid [321].

Dopamine is very active on the crayfish stretch receptor neuron [322], which has been used as a standard for bioassays of inhibitors such as γ-aminobutyric acid. A number of other unknown compounds with similar activities, such as γ-hydroxybutyric acid, are present in brain extracts [323]. However, many more interrelations will have to be uncovered before the complex pattern of subtle and balanced interplay of central amines will be complete.

VII. Endogenous Amines in Health and Disease

Catecholamines and serotonin are intimately linked to brain function. Aberrations in their metabolism would be expected to lead to abnormal conditions or pathological syndromes. A clear case of such an aberration and pathologic state is phenylketonuria, in which the enzyme phenylalanine hydroxylase is absent [324]. Various metabolites, such as amino acids, keto acids, and keto amines, accumulate in the phenylketonuric patient, but it is not known at present which of these, in a positive or negative way, is responsible for his mental degeneration. Other diseases of the central nervous system are caused by metabolic disorders of amino acids (Table 1).

Table 1. The metabolic basis of certain mental disorders [324a]

Syndrome	Genetic defect	Pathological condition
Phenylketonuria	Lack of phenylalanine hydroxylase	Mental deficiency
Maple syrup disease (Leucinosis)	Lack of keto acid decarboxylase for leucine, isoleucine and valine	Cerebral degeneration
Hartnups disease (Congenital pellagra)	Defect in jejunal and renal transport of tryptophan	Mental deficiency
Histidinemia	Lack of histidase	Speech defects
Cystathionuria	Defect in cystathionine metabolism	Mental deficiency

A more complicated syndrome is Parkinson's disease, which affects the extrapyramidal system of the brain, *i.e.* a region characterized by a high concentration of dopamine. Sufferers from Parkinson's disease show lower levels of dopamine in this region of the brain [325], excrete less dopamine into the urine [326], and occasionally improve after the administration of dopa [327]. However, other workers have reported normal levels of dopamine metabolites [328] and little improvement with dopa [329]. The relation of dopamine to Parkinsonism has been critically reviewed [330].

Analysis of schizophrenia in biochemical terms is much more complicated and still in the initial and largely hypothetical state [331, 332]. Two lines of evidence have encouraged the belief that changes in the subtle balance of pharmacodynamic amines in the brain are involved in the etiology and characterization of schizophrenia. On the one hand, drugs that are known to affect brain amines are also effective in the treatment of mental patients. On the other hand, schizophrenic effects are produced by psychotomimetic substances which bear a structural resemblance to endogenous amines [333]. Paramount among these are *N,N*-diethyllysergamide *(93)*, which is effective in minute amounts [334], and mes-

[310] *J. H. Welsh*, Fed. Proc. *13*, 162 (1954).

[311] *D. W. Woolley*, Proc. nat. Acad. Sci. USA *46*, 923 (1960).

[312] *P. Gordon, F. J. Haddy*, and *M. A. Lipton*, Science (Washington) *128*, 531 (1958).

[313] *P. Gordon, F. Haddy*, and *M. A. Lipton*, Fed. Proc. *18*, 397 (1959).

[314] *G. M. Roth* and *W. F. Kvale*, Amer. J. med. Sci. *210*, 653 (1945).

[315] *O. Eichler* and *F. Barfuss*, Arch. exp. Pathol. Pharmakol. *140*, 156 (1940).

[316] *W. Feldberg* and *A. N. Smith*, Brit. J. Pharmacol. Chemotherapy *8*, 406 (1953).

[317] *P. Z. Nirenberg* and *S. Udenfriend*, unpublished results.

[318] *W. Haefely* and *A. Hürlimann*, Experientia *18*, 297 (1962); *H. Zuber* and *R. Jaques*, Angew. Chem. *74*, 216 (1962); Angew. Chem. internat. Edit. *1*, 160 (1962).

[319] Inhibition in the Nervous System and Gamma-Aminobutyric Acid. Pergamon Press, New York 1960.

[320] *J. J. Pisano, J. D. Wilson, L. Cohen, D. Abraham*, and *S. Udenfriend*, J. biol. Chemistry *236*, 499 (1961).

[321] *J. J. Pisano, D. Abraham*, and *S. Udenfriend*, Arch. Biochem. Biophysics *100*, 323 (1963).

[322] *E. G. McGeer, P. L. McGeer*, and *H. McLennan*, J. Neurochemistry *8*, 36 (1961).

[323] *S. P. Bessman* and *W. N. Fishbain*, Fed. Proc. *22*, 334 (1963).

[324] *S. Udenfriend*, Amer. J. clin. Nutrit. *9*, 691 (1961); *F. L. Lyman:* Phenylketonuria. Thomas, Springfield, Ill., 1963.

[324a] *J. B. Stauburg, D. S. Frederickson*, and *J. B. Wyngaarden*: The Metabolic Basis of Inherited Disease. McGraw-Hill, New York 1960.

[324b] *T. L. Sourkes:* Biochemistry of Mental Disease. Harper and Rowe, New York 1962.

[325] *H. Ehringer* and *O. Hornykiewicz*, Klin. Wschr. *38*, 1236 (1960).

[326] *A. Barbeau, G. Jasmin*, and *Y. Duchastel*, Neurology *13*, 56 (1963).

[327] *A. Barbeau*, VIIth Int. Congress of Neurology, Rome, Sept. 1961.

[328] *P. L. McGeer* and *C. M. Williams*, Neurology *23*, 73 (1963).

[329] *P. L. McGeer, J. E. Boulding, W. C. Gibson*, and *R. G. Foulks*, J. Amer. med. Assoc. *177*, 665 (1961).

[330] *O. Hornykiewicz*, German Medical Monthly *7*, 344 (1962).

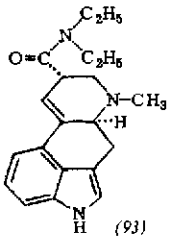
[331] *J. R. Smythies*, Lancet *1958*, II, 308; *1960*, I, 1287.

[332] *S. S. Kety*, Science (Washington) *129*, 1528, 1590 (1959).

[333] *D. F. Downing*, Quart. Rev. (London) *16*, 133 (1962).

[334] *W. A. Stoll*, Schweiz. Arch. Neurol. Neurochir. Psychiat. *60*, 279 (1947).

caline *(94)*, which is effective only in comparatively large doses, an observation which led investigators to search for an active metabolite [159, 335–339a].



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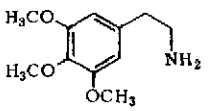


(94)

Much of the research in schizophrenia has been directed toward differences between schizophrenics and normal controls, an approach which is fraught with all the difficulties of prior medical history, drug therapy, physical condition, diet, and other extraneous contingencies. Thus, urinary differences may often reflect lack of suitable controls rather than biochemical patterns of schizophrenia. Recent claims for the occurrence of bufotenine [340], 3,4-dimethoxyphenethylamine [341] and *N*-methylmetanephrine [52] have now to be added to the list of "urinary metabolites" of schizophrenics.

Administration of tryptophan combined with inhibition of MAO produces psychoses in normal patients [304]. In schizophrenics, administration of both tryptophan (precursor of serotonin) and methionine (source of methyl for COMT), combined with inhibition of MAO sometimes leads to an exacerbation of mental symptoms[342].

VIII. Epilogue: Mental Biochemistry and Control of the Mind

Confrontation of biochemistry with the complexities of mental disorders has led to a number of successes, if not always culminating in the elucidation of mechanisms, then at least providing a rational basis for therapy. Those who are still disheartened at the dim prospects for a comprehensive description of the vaguely defined syndrome [343] of schizophrenia in exact biochemical terms [332] would do well to contemplate the words of *Thudichum*, the father of modern brain chemistry, written in 1897 [344]: "Meine ärztliche Seele hängt, in Dichterworten ausgedrückt, mit herber Liebeslust an der Unfehlbarkeit der chemischen Methode. Sie war mir ein spiritus rector in dem bewegten Meer der ärztlichen Konjektur, auf welchem man so häufig jedes Kompasses entbehrt. In Gemeinschaft mit der Entwicklung der Aetiologie und Diagnostik hat die chemische Methode der Erforschung und Behandlung der Krankheit in mir die Überzeugung genährt, daß die Heilkunst, abgesehen von ihrer Ausübung durch das Genie und seine Herrschaft über die menschlichen Gemüter, einer Ausbildung zu einer vollkommenen Wissenschaft und einer Anwendung zu einer fast astronomischen Genauigkeit fähig ist. Dazu müssen aber, wie in der Theologie die Fälschungen der Urkunden, so in der Medizin, um mich eines Ausdrucks von Darwin zu bedienen, die 'falschen Thatsachen' ausgereutet und die wissenschaftlichen Bestände für die Einsicht aller Intelligenzen festgestellt werden" [*]. *Thudichum*'s prophesy [344]: "Der Zusammenhang von Störungen des Hirns mit anomalen chemischen Vorgängen des Körpers läßt sich zunächst nur durch die feinste chemische Diagnose nachweisen, ehe die Krankheit sich durch massive Resultate manifestiert" [**] has been amply fulfilled, for instance in the case of phenylketonuria.

Psychopharmacology and psychotherapy have now become accepted terms and disciplines [345]. Mental biochemistry and scientific exploration of the mind [345] touch on problems on a higher level of interdisciplinary organization. The term "control of the mind" [346] has a ring of ominous timeliness. To some, it seems to express an aim attainable by the use of psychotropic drugs. To others, experience and education appear to be much stronger forces for controlling the mind than any pharmaca, such as *Aldous Huxley*'s Soma of "Brave-New-World" fame. "If we ever permit a state of affairs to develop in which a drug can be fed to large populations for the purpose of controlling their minds, f submit that control of the mind will already have been achieved, and the drug itself need be no more than a placebo"[347].

The authors are greatly indebted to Drs. J. Axelrod and I. J. Kopin for a critical perusal of the manuscript.

Received, April 16th, 1963 [A 304/100 IE]
German version: Angew. Chem. *75*, 552 (1963).

[335] *J. Harley-Mason, A. H. Laird*, and *J. R. Smythies*, Confinia Neurol. *18*, 152 (1958).

[336] *L. C. Mokrasch* and *I. Stevenson*, J. Nervous Mental Disease *129*, 177 (1959).

[337] *J. Ratcliffe* and *P. Smith*, Chem. and Ind. *1959*, 925.

[338] *M. Goldstein, A. J. Friedhoff, S. Pomerantz, C. Simmons*, and *J. F. Contrera*, J. Neurochemistry *6*, 253 (1961).

[339] *A. J. Friedhoff* and *M. Goldstein*, Ann. New York Acad. Sci. *96*, 5 (1962).

[339a] *N. H. Neff* and *G. V. Rossi*, Fed. Proc. *22*, 335 (1963).

[340] *E. Fischer, F. A. Vázquez, T. A. Fernández*, and *L. Liskowski*, Lancet *1961*, I, 890.

[341] *A. J. Friedhoff* and *E. VanWinkle*, J. Nervous Mental Disease *135*, 550 (1962).

[342] *W. Pollin, P. V. Cardon Jr.*, and *S. S. Kety*, Science (Washington) *133*, 104 (1961).

[343] *H. Brill*, Ann. New York Acad. Sci. *96*, 487 (1962).

[344] *J. L. W. Thudichum:* Die Chemische Konstitution des Gehirns. Franz Pietzcker, Tübingen 1901, pp. V–VI.

[*] My soul as a physician, to express it poetically, clings like a love-lorn swain to the idol of the infallability of the chemical method which was the lodestar guiding me through the troubled sea of medical conjecture, where one is so often cast adrift without a compass. Coupled with the development of etiology and diagnostics, the chemical method of investigating and treating diseases fostered the conviction within me that, beside its practice by the genius, with his sway over human temperaments, the medical art could be evolved into an exact science to be applied with almost astronomical certainty. However, to secure this aim, then just like in theology, apocrypha, in medicine, all "false facts" – to use *Darwin*'s term – have to be eradicated, and the fund of scientific knowledge secured for the scrutiny of the intelligentia.

[**] The connection between mental disorders and anomalous chemical processes in the body can be detected only by the most sensitive of chemical methods during the early stages before the disease manifests itself in pronounced symptoms.

[345] Cf. Ann. New York Acad. Sci. *66*, 417–840 (1957).

[346] Cf. *S. M. Farber* and *R. H. L. Wilson:* Man and Civilization: Control of the Mind. McGraw Hill, New York 1961.

[347] *S. Kety*, [346] p. 91.

The Biosynthesis of Alkaloids II [*]

BY PROFESSOR DR. K. MOTHES AND DOZENT DR. H. R. SCHÜTTE

DEUTSCHE AKADEMIE DER WISSENSCHAFTEN ZU BERLIN
INSTITUT FÜR BIOCHEMIE DER PFLANZEN, HALLE/SAALE (GERMANY)

I. Isoquinoline alkaloids
1. Isoquinoline protoalkaloids
2. True isoquinoline alkaloids
a) Biogenesis of the isoquinoline system
b) Biogenesis of the morphine structure
c) Alkaloids derived from benzylisoquinoline
d) Berberine alkaloids
e) Phthalidylisoquinolines
f) Benzophenanthridine alkaloids
3. Alkaloids from *Amaryllidaceae*
4. Colchicine
5. Gliotoxin

II. Indole alkaloids
1. Tryptamine derivatives
2. Gramine
3. Carboline derivatives
4. Yohimbine, cinchonine, and strychnine
5. Ajmaline, serpentine, and reserpine
6. Ergot alkaloids

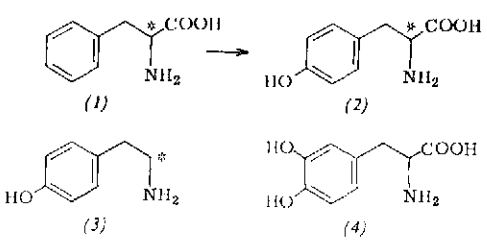
III. Anthranilic acid family
1. Damascenine
2. Quinoline and quinazoline alkaloids

IV. Miscellaneous

V. Summary

I. Isoquinoline Alkaloids

The isoquinoline alkaloids include many compounds with very diverse botanic-taxonomic occurrence and with structures that are sometimes quite complicated. Even in early papers [1,2], the biosynthesis of these alkaloids from the aromatic amino acids phenylalanine *(1)*, tyrosine *(2)*, and dihydroxyphenylalanine *(4)* was already discussed.

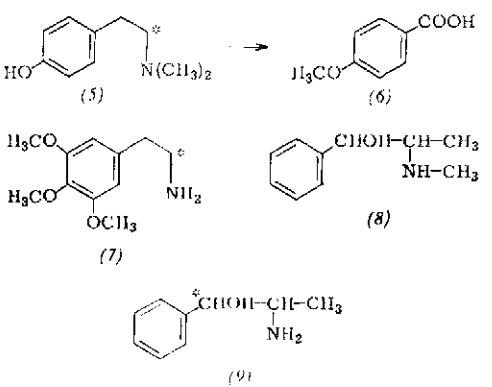


(1) *(2)* *(3)* *(4)*

1. Isoquinoline Protoalkaloids

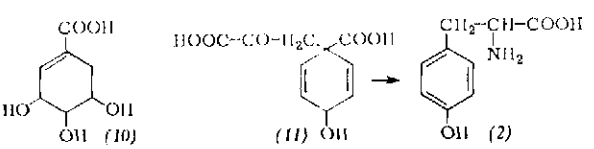
Hordenine *(5)*, mescaline *(7)*, and ephedrine *(8)* are members of this group.

Experiments with radioactively labelled compounds have shown that, in barley, [2-^{14}C]phenylalanine *(1)* [3] [1-^{14}C]tyramine *(3)* [4], and [2-^{14}C]tyrosine *(2)* [5] can be converted into hordenine *(5)* and *N*-methyltyramine [tyramine = *(3)*]. It was demonstrated by degradation to inactive anisic acid *(6)* and trimethylamine that the radioactivity, as expected, was localized specifically in position 1 of the hordenine *(5)* (marked with an asterisk). The authors therefore concluded that tyramine *(3)*



(5) *(6)* *(7)* *(8)* *(9)*

is normally formed from phenylalanine via tyrosine; however, in buckwheat and wheat [6], and also in *Escherichia coli* [7], phenylalanine and tyrosine can also originate from prephenic acid by separate pathways. The main biosynthetic route would then be shikimic acid *(10)* → prephenic acid *(11)* → tyrosine *(2)* and then on to tyramine *(3)*.



(10) *(11)* *(2)*

Quantitative studies have shown that hordenine *(5)* is formed from tyramine by stepwise methylation proceeding via *N*-methyltyramine. Tracer studies have shown

[*] Part I of this review appeared in Angew. Chem. internat. Edit. *2*, 341 (1963).

[1] *G. Trier:* Über einfache Pflanzenbasen und ihre Beziehungen zum Aufbau der Eiweißstoffe und Lecithine. Gebr. Borntträger, Berlin 1912, p. 117.

[2] *R. Robinson*, J. chem. Soc. (London) *111*, 762, 876 (1917); The Structural Relations of Natural Products. Clarendon Press, Oxford 1955.

[3] *J. Massicot* and *L. Marion*, Canad. J. Chem. *35*, 1 (1957).

[4] *E. Leete, S. Kirkwood*, and *L. Marion*, Canad. J. Chem. *30*, 749 (1952).

[5] *E. Leete* and *L. Marion*, Canad. J. Chem. *31*, 126 (1953).

[6] *O. L. Gamborg* and *A. C. Neish*, Canad. J. Biochem. Physiol. *37*, 1277 (1959); cf. also *J. Massicot* and *L. Marion*, Canad. J. Chem. *35*, 1 (1957); *A. C. Neish*, Ann. Rev. Plant. Physiol. *11*, 55 (1960).

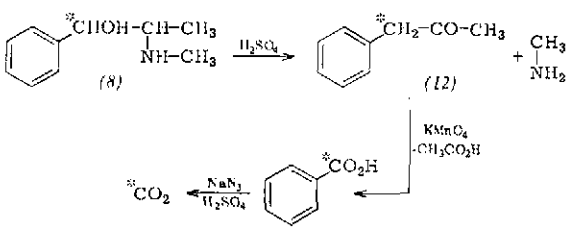
[7] *I. Schwinck* and *E. Adams*, Biochim. biophysica Acta *36*, 102 (1959); *B. D. Davis*, Arch. Biochem. Biophysics *78*, 497 (1958).

that methionine [8] and betaine [9] are the methyl-group donors. This methylation is partially reversible [10]. Using [2-^{14}C]tyrosine, it was shown that [2-^{14}C]tyrosine is also a specific precursor of mescaline *(7)* [11]. Oxidation resulted in inactive trimethoxybenzoic acid; thus, all of the radioactivity was in carbon atom 1 (asterisk) of the mescaline *(7)*.

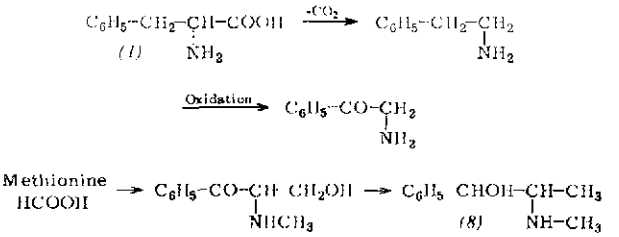
Ephedrine *(8)* and norpseudoephedrine *(9)* differ from the simple phenethylamines discussed so far in having an aliphatic hydroxyl and a *C*-methyl group, which can be assumed to originate by reduction of the carboxyl group or by *C*-methylation of a phenethylamine derivative.

In *Ephedra distachya*, [^{15}N]phenylalanine is incorporated specifically into ephedrine, while [^{15}N]alanine does not act as a precursor [12]. This important result indicates that, in all likelihood, nitrogen is incorporated into the alkaloid directly with the phenylalanine structure, and does not become incorporated into ephedrine by transamination after having first entered the general nitrogen pool. If the latter were the case, a larger fraction of the nitrogen from the alanine would also have been incorporated.

The fact that [3-^{14}C]phenylalanine can be incorporated specifically into norpseudoephedrine *(9)* in *Catha edulis* is in agreement with these findings [13]. After oxidation of this compound to benzoic acid and subsequent decarboxylation, all of the radioactivity was, as expected, found in the carboxyl group of the benzoic acid or in the carbon dioxide corresponding to the carbon atom of the norpseudoephedrine *(9)* marked with an asterisk. In further experiments, *Shibata* et al. showed that [β-^{14}C]-acetophenone was incorporated specifically into ephedrine *(8)* [14]. After decomposition via methyl benzyl ketone *(12)*, all of the radioactivity was located in the carboxyl group of benzoic acid.



Methionine can furnish the *N*-methyl group of ephedrine [15]. The *C*-methyl group of the ephedrine does not originate from the carboxyl group of phenylalanine; however, [^{14}C]formate can be incorporated at this position, so that it must be assumed that addition of a C_1-fragment has occurred after decarboxylation of the amino acid [16]. Scheme 1 summarizes the results of the biogenesis of ephedrine [8], starting with phenylalanine *(1)*.



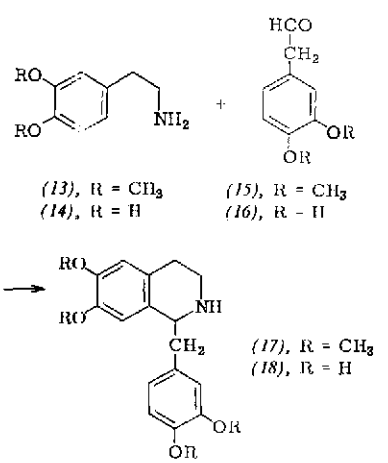
Scheme 1. Biogenesis of ephedrine *(8)* from phenylalanine *(1)*.

The sequence of the individual steps should not be considered as fixed. The scheme resembles the biogenesis of adrenaline and noradrenaline [17].

2. True Isoquinoline Alkaloids

a) *Biogenesis of the Isoquinoline System*

Such complex compounds as morphine and its derivatives, the berberine alkaloids, the *Chelidonium* alkaloids, and others belong to the true isoquinoline alkaloids. The most important reaction in the biogenesis of these compounds is the condensation of a phenethylamine derivative *(13)* with a phenylacetaldehyde derivative *(15)* – both of which are derived from phenylalanine – or with other aldehydes to form isoquinoline derivatives. As far back as 1910, on the basis of structural relationships to phenylalanine, *Winterstein* and *Trier* [18] proposed that the biosynthesis of tetrahydropapaverine *(17)*, and of its *N*-methyl compound, laudanosine, which occurs in opium, starts with β-(3,4-dimeth-



(13), R = CH_3 *(15)*, R = CH_3
(14), R = H *(16)*, R = H

(17), R = CH_3
(18), R = H

[8] *S. Kirkwood* and *L. Marion*, Canad. J. Chem. *29*, 30 (1951); *T. J. Matchett*, *L. Marion*, and *S. Kirkwood*, Canad. J. Chem. *31*, 488 (1953); *E. Leete* and *L. Marion*, Canad. J. Chem. *32*, 646 (1954); *S. H. Mudd*, Biochim. biophysica Acta *37*, 164 (1960).

[9] *M. Sribney* and *S. Kirkwood*, Canad. J. Chem. *32*, 918 (1954).

[10] *A. W. Frank* and *L. Marion*, Canad. J. Chem. *34*, 1641 (1956).

[11] *E. Leete*, Chem. and Ind. *1959*, 604.

[12] *S. Shibata* and *I. Imaseki*, Pharmac. Bull. (Tokyo) *4*, 277 (1956).

[13] *E. Leete*, Chem. and Ind. *1958*, 1088.

[14] *I. Imaseki*, *S. Shibata*, and *M. Yamazaki*, Chem. and Ind. *1958*, 1625.

[15] *S. Shibata*, *I. Imaseki*, and *M. Yamazaki*, Pharmac. Bull. (Tokyo) *5*, 71 (1957).

[16] *S. Shibata*, *I. Imaseki*, and *M. Yamazaki*, Pharmac. Bull. (Tokyo) *5*, 594 (1957).

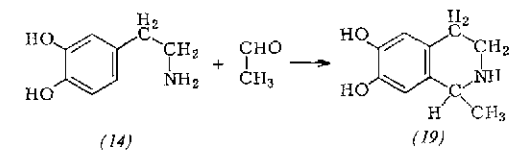
[17] *S. Udenfriend* and *J. B. Wyngarden*, Biochim. biophysica Acta *20*, 48 (1956); *M. Goodall* and *N. Kirshner*, J. biol. Chemistry *226*, 213 (1957); *N. Kirshner*, ibid. *226*, 821 (1957); *G. Rosenfeld*, *L. C. Leeper*, and *S. Udenfriend*, Arch. Biochem. Biophysics *74*, 252 (1958); *H. Blaschko*, Brit. Med. Bull. *13*, 162 (1957); *S. Senoh*, *C. R. Creveling*, *S. Udenfriend*, and *B. Witkop*, J. Amer. chem. Soc. *81*, 6236 (1959).

[18] *E. Winterstein* and *G. Trier:* Die Alkaloide. Gebr. Borntträger, Berlin 1910, p. 307.

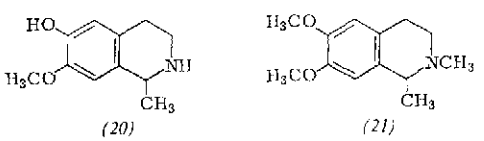
oxyphenyl)ethylamine *(13)* and 3,4-dimethoxyphenylacetaldehyde *(15)* and proceeds byaldehyde-ammonia formation and condensation with a hydrogen atom in *para*-position to one methoxy group.

This hypothesis has been found very useful for the various isoquinoline alkaloids [19–21]. It has proved possible to carry out these condensations under physiological conditions [19,22], provided the phenethylamine moiety contains a free hydroxyl group in *para*-position to C-6 of the benzene ring; the fully methylated compounds react only very slowly [23].

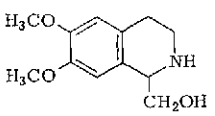
Thus, if a salt of β-(3,4-dihydroxyphenyl)ethylamine *(14)* is allowed to react with acetaldehyde in aqueous solution at pH 5 for three days at 25 °C [24], a compound *(19)* is obtained in practically quantitative yield which can be regarded as the precursor of the naturally occurring bases salsoline *(20)* and carnegine *(21)* inasmuch as methylation at the oxygen or nitrogen groups could readily take place *in vivo*. Calycotomine *(22)* was prepared similarly [25].



(14) *(19)*

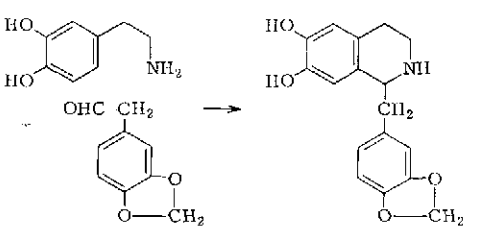


(20) *(21)*



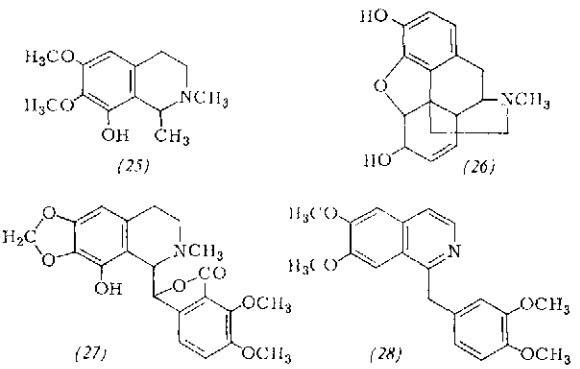
(22)

If homopiperonal *(23)* is used instead of acetaldehyde, the product is the benzylisoquinoline derivative *(24)* [26].



(23) *(24)*

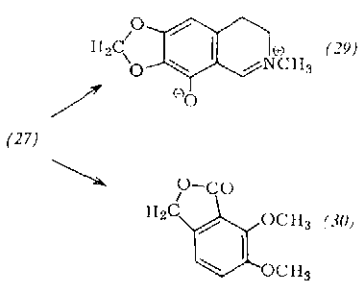
This hypothesis concerning the biosynthesis of isoquinoline alkaloids was confirmed using radioactively labelled compounds. [2-^{14}C]Tyrosine can serve as a precursor of the simple isoquinoline alkaloid pellotine *(25)* in *Lophophora williamsii* [27]. Again, when uniformly labelled [^{14}C]-L-tyrosine was applied to isolated leaves or isolated immature pods, a considerable amount of radioactivity was always detected in the alkaloids of *Papaver somniferum*, viz. morphine *(26)*, codeine, thebaine, narcotoline *(27)*, narcotine, and papaverine *(28)* [28].



(25) *(26)*

(27) *(28)*

The radioactive narcotoline *(27)* obtained was split into cotarnoline *(29)* and meconine *(30)*; the former contained 52 % and the latter 48 % of the radioactivity. This result indicates that narcotoline is formed from two molecules of tyrosine, in accordance with the theoretical concepts discussed above. However, narcotoline *(27)* already possesses one more carbon atom than the simple benzylisoquinoline alkaloids. We shall discuss this type of phthalidylisoquinoline derivative further below (see Section I, 2e).



(27) *(29)* *(30)*

By administering [2-^{14}C]tyrosine to *Papaver somniferum* and degrading the radioactive papaverine *(28)* obtained, it was confirmed that the benzylisoquinoline structure originated specifically (as shown by the asterisks) from two molecules of tyrosine *(2)*, probably via norlaudanosoline *(18)* [29]. The degradation proceeded via laudanosoline *(31)*. The latter was subjected to Hofmann degradation; the resulting amine *(32)* formed the acid *(33)* on oxidation and repeated Hofmann degradation; the resulting acid contained all of the radioactivity.

[19] *Cl. Schöpf*, Angew. Chem. *50*, 779, 797 (1937).

[20] *R. Robinson*: The Structural Relations of Natural Products. Clarendon Press, Oxford 1955.

[21] *L. Marion*, Angew. Chem. *66*, 568 (1954); J. chem. Soc. (London) *1954*, 2987.

[22] *G. Hahn* and *K. Stiehl*, Ber. dtsch. chem. Ges. *69*, 2627 (1936); *G. Hahn* and *F. Rumpf*, ibid. *71*, 2141 (1938).

[23] *G. Hahn* and *O. Schales*, Ber. dtsch. chem. Ges. *68*, 25 (1935); *E. Späth*, *F. Kuffner*, and *F. Keszler*, ibid. *69*, 378 (1936); *70*, 1017 (1937).

[24] *Cl. Schöpf* and *H. Bayerle*, Liebigs Ann. Chem. *513*, 190 (1934).

[25] *A. Chatterjee* and *N. A. Chaudhury*, Sci. and Cult. (Calcutta) *25*, 389 (1959); Chem. Zbl. *132*, 10946 (1961).

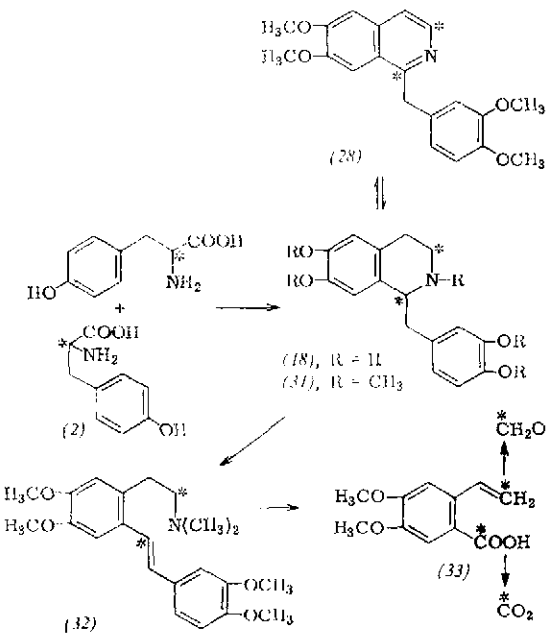
[26] *Cl. Schöpf* and *W. Salzer*, Liebigs Ann. Chem. *544*, 1 (1940).

[27] *A. R. Battersby* and *S. Gavrat*, Quart. Rev. (Chem. Soc., London) *15*, 272 (1961).

[28] *G. Kleinschmidt* and *K. Mothes*, Z. Naturforsch. *14b*, 52 (1959).

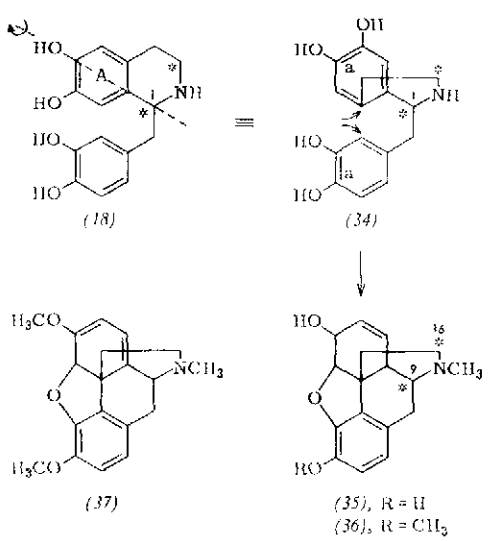
[29] *A. R. Battersby* and *B. J. T. Harper*, Proc. chem. Soc. (London) *1959*, 152; *A. R. Battersby* and *B. J. T. Harper*, J. chem. Soc. (London) *1962*, 3526.

Ozonolysis yielded formaldehyde which had almost half of the radioactivity; the other half was contained in carbon dioxide produced on decarboxylation.

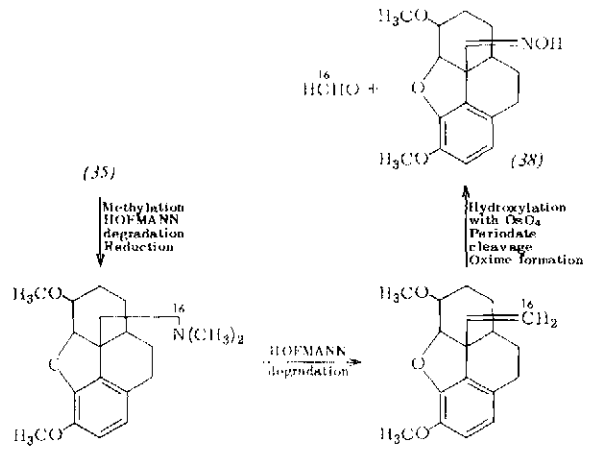


b) *Biogenesis of the Morphine Skeleton*

According to the theory of *Robinson* and *Gulland* [30], norlaudanosoline *(18)* should also be an intermediate on the biosynthetic pathway to morphine *(35)* and its derivatives, *e.g.* codeine *(36)*, and thebaine *(37)*. If norlaudanosoline *(18)* is written as in *(34)*, where ring A is merely rotated about the dotted line, then the relationship to morphine *(35)* immediately becomes apparent. After administration of [2-^{14}C]tyrosine, morphine would be expected to be labelled in the positions denoted by the asterisks in *(35)*.

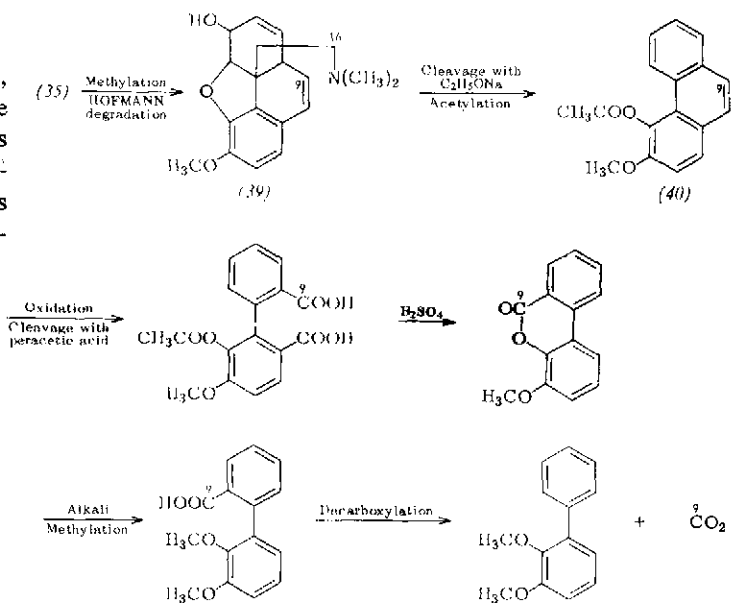


This hypothesis was verified with the aid of [2-^{14}C]tyrosine. In addition to labelling papaverine, already mentioned, the experiment also led to labelled morphine *(35)* [28,31,32], codeine *(36)* [33], and thebaine *(37)* [33]. It was established by degradation of morphine [34] that the radioactivity was confined to carbon atoms 9 and 16, C-16 being the first to be isolated (Scheme 2a) [31].



Scheme 2a. Degradation of morphine *(35)* leading to isolation of carbon atom 16.

The resulting formaldehyde and the residual moiety *(38)* each contained half of the radioactivity. In another degradation [35], carbon atom 9 was isolated (Scheme 2b).



Scheme 2b. Degradation of morphine *(35)* leading to isolation of carbon atom 9.

The resulting carbon dioxide, which represents the carbon of C-9 of the morphine molecule, again possesses half of the specific activity of the morphine molecule. This result was confirmed independently [36], whereby the *N*,*N*-dimethyl ethanolamine *(41)* obtained from

[30] *J. M. Gulland* and *R. Robinson*, Mem. Proc. Manchester lit. philos. Soc. *69*, 79 (1925).

[31] *A. R. Battersby* and *B. J. T. Harper*, Chem. and Ind. *1958*, 364.

[32] *E. Leete*, Chem. and Ind. *1958*, 977.

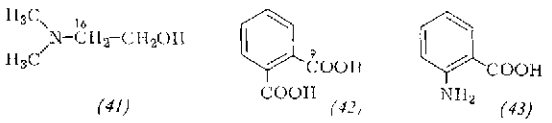
[33] *A. R. Battersby* and *B. J. T. Harper*, Tetrahedron Letters *1960*, No. 27, 21.

[34] *A. R. Battersby*, *R. Binks*, and *B. J. T. Harper*, J. chem. Soc. (London) *1962*, 3534.

[35] *A. R. Battersby*, *R. Binks*, and *D. J. Le Count*, Proc. chem. Soc. (London) *1960*, 287.

[36] *E. Leete*, J. Amer. chem. Soc. *81*, 3948 (1959).

compound *(39)* and the phthalic acid *(42)* resulting from oxidation of the phenanthrene derivative *(40)* each accounted for half of the radioactivity in the original morphine. The anthranilic acid *(43)* resulting from Schmidt degradation of the phthalic acid was half as radioactive as the phthalic acid.



(41) *(42)* *(43)*

From the foregoing it may be considered certain that the complicated morphine system can be synthetized from two molecules of tyrosine. [2-^{14}C]Phenylalanine was utilized to a lesser degree than [2-^{14}C]tyrosine [34,36]. This result again points to the series shikimic acid → prephenic acid → tyrosine; phenylalanine is possibly on a by-pass and must first be converted into tyrosine. That the biosynthesis of morphine actually proceeds via norlaudanosoline *(18)* seems probable because of the exceedingly high degree of incorporation of this precursor *(34)* when labelled in position 1 into the morphine molecule *(35)* [37]. After degradation, all of the radioactivity was located in C-9 of the morphine molecule [38]. This shows that plants can carry out oxidative coupling [20,39,40] at the two positions of the norlaudanosoline system *(34)* indicated by arrows to yield the morphine system *(35)*, a reaction which has been unsuccessfully attempted in the laboratory many times [39, 41]. There are several hypotheses concerning this coupling [20,40,42–44]. [1-^{14}C]Norlaudanosoline *(34)* is also specifically incorporated into papaverine *(28)* [38]. This means that plants are also capable of aromatizing tetrahydroisoquinoline *(34)*.

The *N*-methyl groups of morphine *(35)*, as well as the *N*- and *O*-methyl groups of codeine *(36)* and thebaine *(37)*, can originate from methionine. Formate has proved to be less effective [45]. A special problem is the natural relationship of the individual alkaloids of the morphine type to each other. In the case of the morphine-codeine alkaloid pair, the methoxyl-free compound, *viz.* morphine *(35)*, may be assumed to be formed first and to be subsequently methylated to give codeine *(36)*. Experiments with radioactively labelled codeine and morphine have shown, however, that codeine can be demethylated to morphine in poppy leaves, but that morphine under these conditions cannot be methylated to codeine [46,47]. Investigation of the degree of incorporation of [^{14}C]carbon dioxide [48] and [2-^{14}C]-tyrosine [33] into morphine *(35)*, codeine *(36)*, and thebaine *(37)* has shown that at first thebaine had the highest degree of labelling followed by codeine and morphine. After a few days, the situation was reversed, *i.e.* morphine was labelled more than codeine and thebaine. From this it can be concluded with some reservation that thebaine is formed first and is then transformed into codeine and morphine, as has already been shown to be true for the codeine-morphine pair [37]. Finally, *Papaver somniferum* was shown to be capable of transforming radioactively labelled thebaine into labelled codeine and morphine, whereas radioactivity from codeine and morphine could not be transferred to thebaine [47]. All of these results indicate that thebaine *(37)* is formed first on the biosynthetic pathway to morphine *(35)*, and that the thebaine is then demethylated to codeine *(36)* and morphine. Comparison of the alkaloid spectra of different *Papaver* species confirms this scheme [47,48]. Thebaine is present in all the *Papaver* species, morphine and codeine in only some. Apparently, not all *Papaver* species are capable of demethylating and hydrogenating thebaine to codeine and morphine. Conceivably, various coupling possibilities are blocked by partial methylation of norlaudanosoline *(34)*, so that thebaine can then be obtained by only one pathway. Norlaudanosoline *(34)* that is partially methylated in the positions denoted by "a" should in theory give rise to thebaine *(37)* quite simply.

Recently, attempts have been made to study the biosynthesis of morphine *(35)* with [^{14}C]carbon dioxide [49]. The incubation time was six hours. As in the degradation procedures mentioned above, the resulting morphine was degraded to both of the postulated tyrosine residues. The ratio of activities of these two fragments varied from 3:2 to 2:1, in contrast to a ratio of almost 1:1 which several authors had found [28, 29,31,34–36] on degradation of the alkaloids obtained after administration of [^{14}C]tyrosine. From the unequal distribution of the radioactivity in the two theoretical tyrosine molecules in morphine, and also in narcotine, the authors [49] concluded that the biosynthetic pathway leading to these alkaloids cannot include the joining of two identical molecules nor can it proceed via a symmetrical intermediate. They even suggest that the biosynthesis of these alkaloids from tyrosine may proceed along only a secondary path and that the actual biosynthesis involves an entirely different pathway. In this connection, reference is made to the fact that considerable amounts of radioactivity from tyrosine can also be incorporated into glucose [50,51]. The latter fact, is however, self-

[37] *A. R. Battersby* and *R. Binks*, Proc. chem. Soc. (London) *1960*, 360.

[38] *A. R. Battersby*, *R. Binks*, and *G. V. Parry*, Quart. Rev. (Chem. Soc., London) *15*, 277 (1961).

[39] *R. Robinson* and *S. Sugasawa*, J. chem. Soc. (London) *1931*, 3163; *1932*, 789; *1933*, 280.

[40] *Cl. Schöpf*, Naturwissenschaften *39*, 241 (1952).

[41] *Cl. Schöpf* and *K. Thierfelder*, Liebigs Ann. Chem. *497*, 22 (1932); *J. Harley-Mason*, J. chem. Soc. (London) *1953*, 1465; *B. Franck*, *G. Blaschke*, and *G. Schlingloff*, Tetrahedron Letters *1962*, No. 10, 439.

[42] *K. W. Bentley*, Experientia *12*, 251 (1956); *G. Storck* and *R. H. F. Manske:* The Alkaloids. Academic Press, New York 1960, Vol. 6, p. 242.

[43] *D. H. R. Barton* and *T. Cohen:* Festschrift für A. Stoll. Birkhäuser, Basel 1957, p. 117.

[44] *T. Cohen*, Chem. and Ind. *1956*, 1391; *D. H. R. Barton*, *A. M. Deflorin* and *O. E. Edwards*, J. chem. Soc. (London) *1956*, 530.

[45] *A. R. Battersby* and *B. J. T. Harper*, Chem. and Ind. *1958*, 365.

[46] *G. Kleinschmidt* and *K. Mothes*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *293*, 948 (1960); *G. Kleinschmidt*, Pharmazie *15*, 663 (1960).

[47] *F. R. Stermitz* and *H. Rapoport*, Nature (London) *189*, 310 (1961); J. Amer. chem. Soc. *83*, 4045 (1961).

[48] *H. Rapoport*, *F. R. Stermitz*, and *D. R. Baker*, J. Amer. chem. Soc. *82*, 2765 (1960).

[49] *H. Rapoport*, *N. Levy*, and *F. R. Stermitz*, J. Amer. chem. Soc. *83*, 4298 (1961).

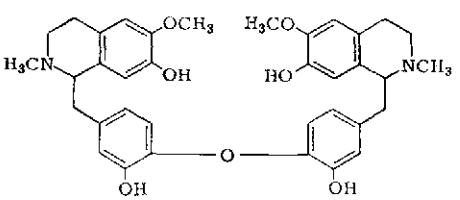
[50] *I. Imaseki*, *R. Oneyama*, and *M. Tajima*, J. pharmac. Soc. Japan *80*, 1802 (1960).

[51] *R. K. Ibrahim*, *S. G. Lawson*, and *G. H. N. Towers*, Canad. J. Biochem. Physiol. *39*, 873 (1961).

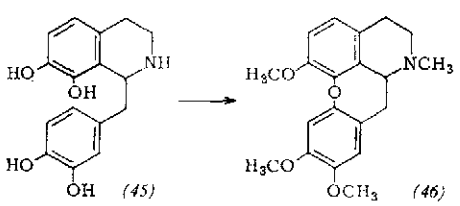
evident. If tyrosine is decomposed at all, specific and non-specific (CO_2!) products would enter into the carbohydrate cycle. We believe that the unequal distribution of activity after this six-hour experiment [49] does not contradict earlier results. The theory postulates formation of the benzylisoquinoline nucleus *(18)* from a phenethylamine derivative *(14)* and a phenylacetaldehyde derivative *(16)*, *i.e.* from two unequally labelled phenylalanine or tyrosine derivatives. This means that an unequal number of reaction steps must have been passed through prior to the synthesis of the true precursors of such a benzylisoquinoline system. We do not know at what rate and in which cell regions these precursors occur, and how large the pool of inactive intermediates is. From these considerations it becomes even probable that the distribution of radioactivity between both tyrosine halves of benzylisoquinoline is unequal in short-term experiments, but approaches a ratio of 1:1 in long-term ones. Deviations from a 1:1 ratio have also been observed in other benzylisoquinoline alkaloids [52, 53] and will be discussed later. It must be remembered that under these conditions, phenylacetaldehyde for example can be formed from the precursor of tyrosine, phenylpyruvic acid, and would not require a detour via tyrosine. Studies to confirm these reactions in detail are still lacking, even though the broad outlines are established; the observation concerning the unequal distribution of radioactivity may represent a first step in this direction.

c) *Alkaloids Derived from Benzylisoquinoline*

A number of alkaloid groups arise from the simple benzylisoquinoline system by a variety of coupling and condensation reactions [20, 21, 43]. Two such benzylisoquinolines may combine in such a way as to yield the large group of the bisbenzylisoquinolines or biscoclaurine alkaloids, for example, aztequine *(44)*. The alkaloids of the cularine group, *e.g.* cularine *(46)*, are obtained by oxidative coupling of an unusual hydroxylated benzylisoquinoline *(45)*. Aporphine alkaloids are also obtained by oxidative coupling of the norlaudanosoline system *(18)*, *e.g.* compounds of the bulbocapnine *(47)*

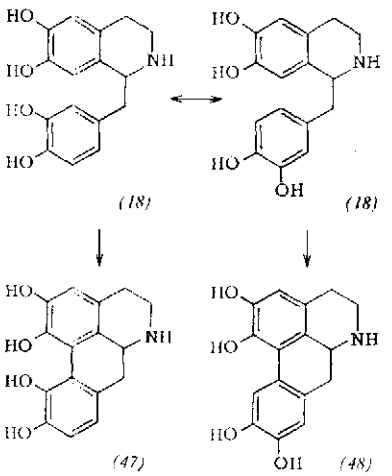


(44)



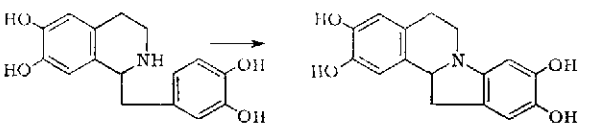
(45) *(46)*

and glaucine types *(48)*. Dibenzopyrrocoline alkaloids *(50)* are obtained by oxidative coupling of the norlaudanosoline system *(49)* with the nitrogen; this reaction has been carried out in the laboratory [39, 41],



(18) *(18)* *(47)* *(48)*

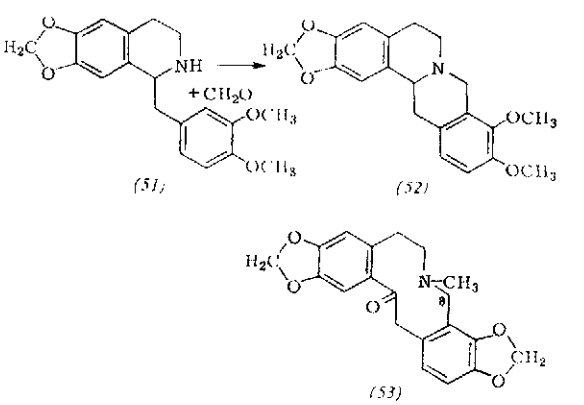
although it is not yet known whether this biogenetic pathway occurs in plants *in vivo*.



(49) = *(18)* *(50)*

d) *Berberine Alkaloids*

Condensation of simple benzylisoquinolines, *e.g.* *(51)*, with a C_1-residue results in the berberine type *(52)*, which has one more ring [20, 21, 54]; this is the parent substance of a very large group of alkaloids. The incorporation of an "active C_1-fragment" in plants is a well-known synthetic step and is promoted by enzymes containing folic acid.



(51) *(52)* *(53)*

This conversion from the benzylisoquinoline type to the berberine type has also been achieved in the laboratory [55]. Alkaloids of the protopine series *(53)* are derived from berberine-type alkaloids by hydrolysis of the bond between the nitrogen atom and the tertiary carbon atom [20, 21]. In the case of protopine *(53)*, it has so far only been shown that the methylenedioxy groups and the *N*-methyl group can originate from the methyl group of methionine. After administration of [*Me*-^{14}C]methio-

[52] *J. R. Gear* and *I. D. Spenser*, Nature (London) *191*, 1393 (1961).

[53] *F. v. Bruchhausen* and *H. W. Bersch*, Ber. dtsch. chem. Ges. *63*, 2520 (1930).

[54] *R. B. Woodward*, Angew. Chem. *68*, 13 (1956).

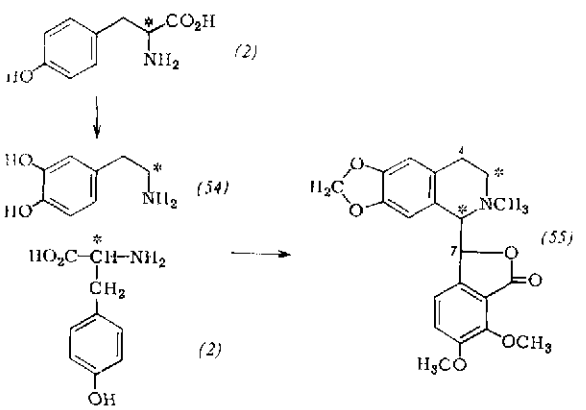
[55] *A. Pictet* and *A. Gams*, Ber. dtsch. chem. Ges. *44*, 2480 (1911); *A. Pictet* and *T. Q. Chou*, ibid. *49*, 370 (1916); *E. Späth* and *E. Kruta*, Mh. Chem. *50*, 341 (1928).

nine, a difference is observed beetwen the radioactivity of the methylenedioxy groups and the *N*-methyl group on the one hand and that of the total alkaloid on the other and is ascribed to carbon atom 8, which is assumed to have been derived from a C_1-moiety [56].

After administration of [2-^{14}C]phenylalanine to *Berberis vulgaris* [57] and of [2-^{14}C]tyrosine to *Coptis japonica* [50], radioactive berberine [type *(52)*] was isolated. [2-^{14}C]Tyrosine was incorporated more extensively into berberine by *Hydrastis canadensis* than was [2-^{14}C]phenylalanine [52]. In this case, the distribution of the radioactivity was in agreement with the theory that berberine is formed from two molecules of tyrosine [58].

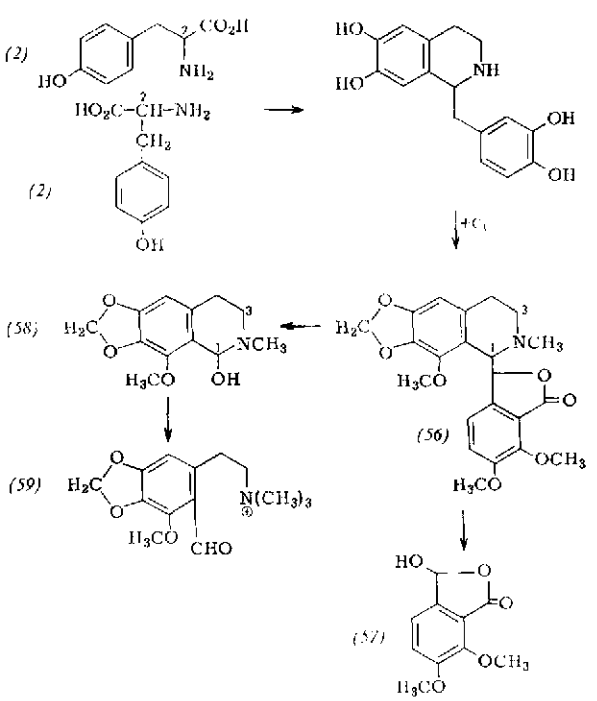
e) *Phthalidylisoquinolines*

The phthalidylisoquinolines, which include narcotoline *(27)*, hydrastine *(55)*, and narcotine *(56)*, are closely related to the berberine alkaloids [20,21]. In connection with papaverine, it has been reported that two molecules of [^{14}C]tyrosine can serve as precursor for narcotoline [28]. Hydrastine can also be biosynthetized specifically by *Hydrastis canadensis* from two molecules of [2-^{14}C]-tyrosine [52]. After an incubation period of 17 days, about 60 % of the radioactivity was located in C-3 and 40 % in C-1. [2-^{14}C]Phenylalanine was less intensively incorporated.



In another experiment with [3-^{14}C]tyrosine, a similar distribution was established after an incubation period of nine days, 57 % being located in C-4 and 43 % in C-7 [59]. The significance of this finding has been discussed above in connection with the biosynthesis of morphine. Interestingly, [2-^{14}C]dopamine *(54)* can form only the isoquinoline ring, all of the radioactivity being located in C-3 [59]. Thus, two moles of tyrosine, but only one mole of dopamine, can be incorporated into hydrastine. On the one hand, the experiments support the classical scheme of biosynthesis [20,21] and fail to support the newer hypothesis [60], according to which prephenic acid *(11)* is thought to be a direct precursor for phthalidylisoquinolines of the hydrastine *(55)* type. On the other hand, because tyrosine shows a higher specific degree of incorporation than dopamine does it has been suggested [59] that dopamine possibly does not lie on the normal biosynthetic pathway to hydrastine *(55)*. With berberine [type *(52)*], the situation is just the reverse; *i.e.* dopamine is incorporated to twice the extent of tyrosine. It is conceivable that there are slightly different alternatives for the biosynthesis of these two alkaloids owing, for example, to differences in the rates of some of the reaction steps. Another possibility is that the syntheses take place in different cell regions which have different permeabilities. It is probable that the amino acid tyrosine and the amine dopamine differ in their ability to permeate the cell or to induce active transport. This makes it difficult to interpret differences in extents of incorporation as necessarily due to differences in biosynthetic pathways. Nevertheless, the results indicate either that *Hydrastis canadensis* cannot oxidatively deaminate dopamine to the corresponding aldehyde, or that the aldehyde moiety used in the physiological-type synthesis is replaced by another derivative which is not formed from dopamine in plants.

The results mentioned above for the biosynthesis of narcotoline *(27)* data were confirmed by experiments in which [2-^{14}C]tyrosine, [1-^{14}C]norlaudanosoline, and [^{14}C]formate were specifically incorporated into narcotine *(56)* by *Papaver somniferum* [61]. The alkaloid was degraded to cotarnine *(58)* and opianic acid *(57)*. Cotarnine is converted into an aldehyde *(59)* by Hofmann degradation. In accordance with theory, the opianic acid *(57)* remained unlabelled after administration of [2-^{14}C]tyrosine, while the cotarnine *(58)* contained 97 % of the radioactivity of the narcotine *(56)*. Each of the carbon atoms 1 and 3 contained about half of the radioactivity. After administration of [1-^{14}C]norlaudanosoline, all of the radioactivity was located in the carbonyl group of the aldehyde *(59)*; after administration of [^{14}C]formate the opianic acid *(57)* contained 48 % of the radioactivity of the alkaloid; 13 % was in the carboxyl group, which according to theory should originate from a C_1-fragment in the same way as the methylene and methyl groups.

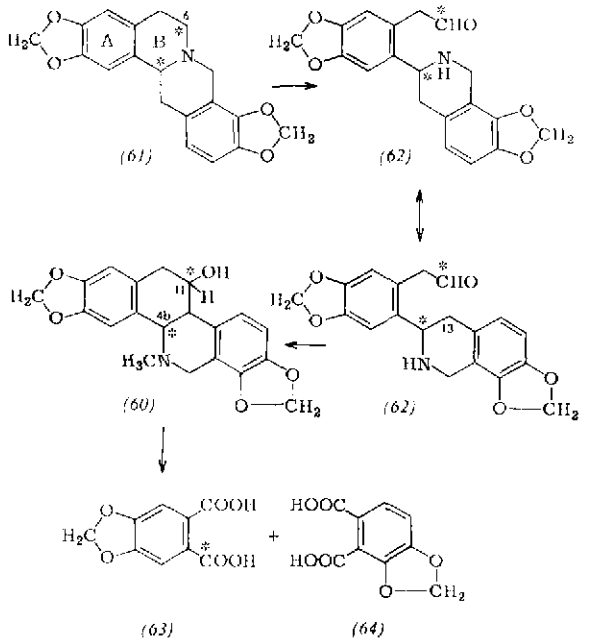


f) *Benzophenanthridine Alkaloids*

The alkaloids of the benzophenanthridine group are also closely related to the berberine alkaloids, and thus to the benzylisoquinolines [20,53]. The formation of chelido-

[56] *M. Sribney* and *S. Kirkwood*, Nature (London) *171*, 931 (1953).
[57] *J. L. Beal* and *E. Ramstad*, Naturwissenschaften *47*, 206 (1960).
[58] *I. D. Spenser* and *J. R. Gear*, Proc. chem. Soc. (London) *1962*, 228.
[59] *I. D. Spenser* and *J. R. Gear*, J. Amer. chem. Soc. *84*, 1059 (1962).
[60] *E. Wenkert*, Experientia *15*, 165 (1959).

nine *(60)* can be represented as follows: stylopine *(61)*, for example, is converted by oxidation at C-6 into an α-hydroxy amine or the tautomeric open-ring amino aldehyde *(62)*. After methylation of the nitrogen, the aldehyde *(62)* is cyclized to chelidonine *(60)* by joining the aldehyde group with C-13.

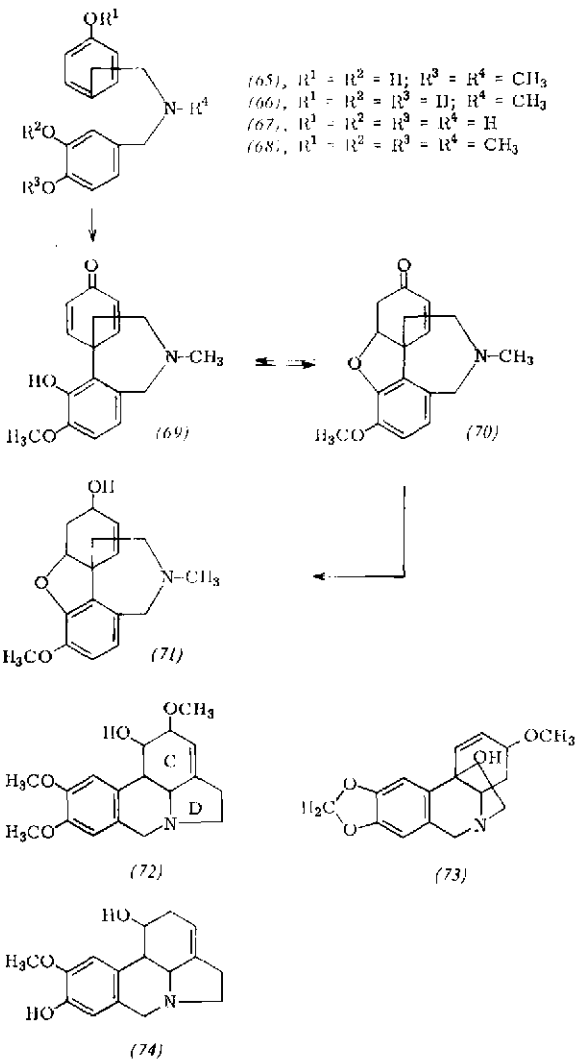


Administration of [2-^{14}C]tyrosine to *Chelidonium majus* resulted in radioactive chelidonine and sanguinarine [62]. Degradation of the chelidonine yielded unlabelled 3,4-methylenedioxyphthalic acid *(64)* and hydrastic acid *(63)* which contained 40% of the radioactivity of the alkaloid (the asterisks again indicate the probable positions of the radioactivity). Since the *N*-methyl group of the chelidonine was inactive, the remaining 60% of the radioactivity must have been located at carbon atom 11. It appears, therefore, that chelidonine can also be synthetized from two molecules of tyrosine, according to the classical biosynthetic scheme; *i.e.* 60% of the radioactivity would be in C-11 [the original isoquinoline moiety; rings A and B in formula *(61)*] and 40% would be in carbon atom 4b (incubation time eight days), as was found in the case of hydrastine [52].

3. Amaryllidaceae Alkaloids

Amine *(68)* has been postulated as a precursor of the *Amaryllidaceae* alkaloids, *e.g.* *(71)* [43]. Amine *(68)* may be considered to be formed from a phenethylamine derivative and a C_6–C_1 moiety. This amine, in turn, may by single or repeated oxidative coupling give rise to a variety of alkaloids, *e.g.* of the galanthamine *(71)*, lycorine *(75)*, haemanthamine *(73)*, or tazettine *(79)* types. However, formation from reduced precursors such as shikimic acid *(10)* and prephenic acid *(11)* has also been suggested [60].

It proved possible to oxidize the amine *(65)* to narwedine *(70)* by chemical synthesis [63], although the yield was poor; reduction of the narwedine yielded galanthamine *(71)* and epigalanthamine. Narwedine *(70)* [64] and belladine *(68)* [65] occur in nature. Both radioactive amine *(65)* and [2-^{14}C]tyrosine were incorporated into galanthamine by King Alfred narcissi [63,66]. Amine *(66)* was also incorporated into galanthamine to the same extent as [2-^{14}C]tyrosine [66]. Norbelladine *(67)* proved to be a precursor of galanthamine *(71)* in snowdrops (*Galanthus elwesii*); of galanthamine *(71)*, galanthine *(72)*, and haemanthamine *(73)* in King Alfred narcissi [66]; of haemanthamine *(73)*, lycorine *(75)*, and norpluviine *(74)* in Twink narcissi [67,68]; and of lycorine *(75)*, crinamine *(73)*, and belladine *(68)* in



[61] *A. R. Battersby* and *D. J. McCaldin*, Proc. chem. Soc. (London) *1962*, 365.

[62] *E. Leete*, Abstracts, 2nd International Symposion on the Chemistry of Natural Products, Prague 1962, p. 75; J. Amer. chem. Soc. 85, 473 (1963).

[63] *D. H. R. Barton* and *G. W. Kirby*, Proc. chem. Soc. (London) *1960*, 392; J. chem. Soc. (London) *1962*, 806.

[64] *H. G. Boit*, *W. Döpke*, and *A. Beitner*, Chem. Ber. *90*, 2197 (1957).

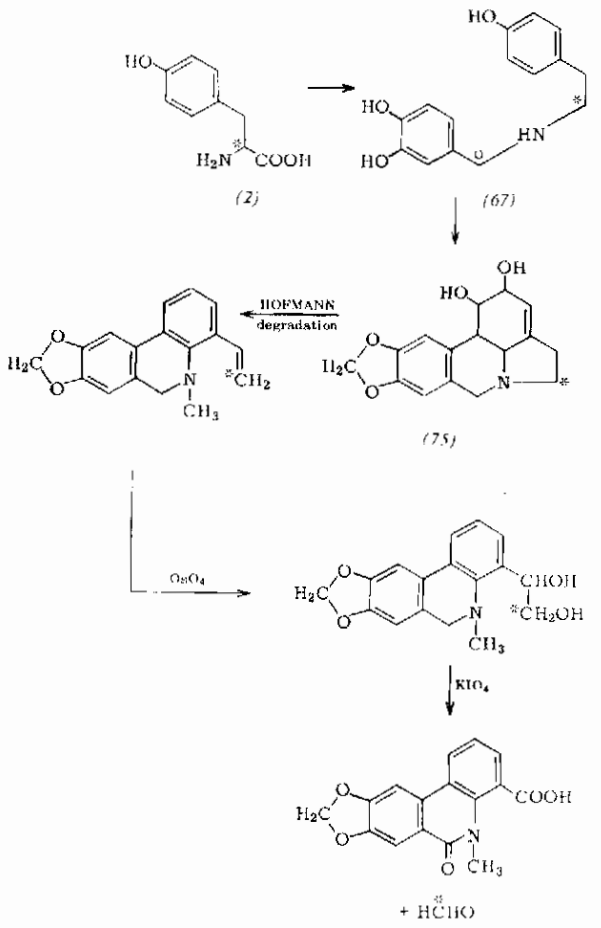
[65] *E. Warnhoff*, Chem. and Ind. *1957*, 1385.

[66] *D. H. R. Barton*, *G. W. Kirby*, *J. B. Taylor*, and *G. M. Thomas*, Proc. chem. Soc. (London) *1961*, 254.

[67] *A. R. Battersby*, *R. Binks*, *S. W. Breuer*, *H. M. Fales* and *W. C. Wildman*, Proc. chem. Soc. (London) *1961*, 243.

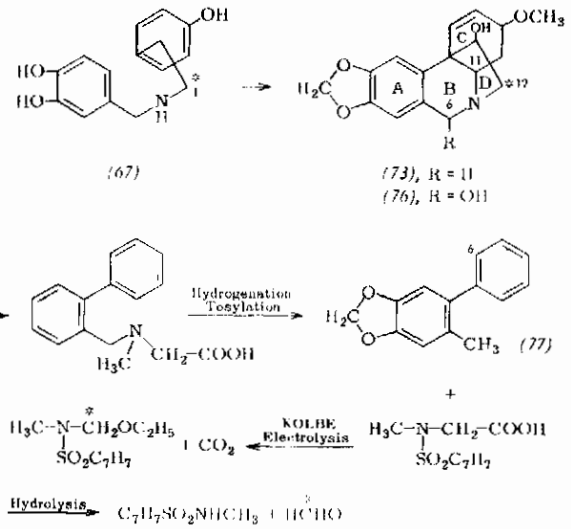
[68] *A. R. Battersby*, *H. M. Fales*, and *W. C. Wildman*, J. Amer. chem. Soc. *83*, 4098 (1961).

Nerine bowdenii [69]. Narcissi incorporate [2-^{14}C]tyrosine into lycorine [63,70], norpluviine [70], and haemanthamine [68,70]. If lycorine *(75)* is derived from tyrosine *(2)* via an amine of the norbelladine type *(67)*, then on administration of [2-^{14}C]tyrosine the activity should recur in the positions marked with asterisks. The formaldehyde resulting from the reactions of Scheme 3 did in fact contain all of the radioactivity of lycorine [70]. Lycorine obtained following administration of [1-^{14}C]norbelladine *(67)* (label denoted by asterisk) contained all of the radioactivity in the carbon atom which was degraded to formaldehyde as shown in Scheme 3. Experiments with doubly labelled norbelladine*(67)* (the carbon atoms denoted by asterisk and circle were labelled) or triply labelled amine *(65)* proved that these molecules were incorporated in their entirity into belladine *(68)*, crinamine *(73)*, and lycorine *(75)* [69]



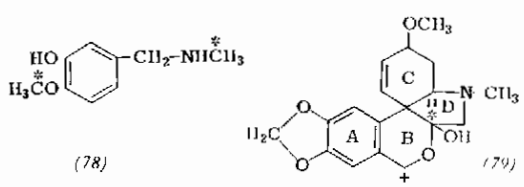
Scheme 3. Biogenesis and degradation of lycorine *(75)*.

or galanthamine *(71)* [71]. The distribution of radioactivity in these alkaloids is similar to that of the original norbelladine, as expected by theory [70]. These results are in agreement with the hypothesis that an intermediate product of the norbelladine type undergoes oxidative coupling to form the lycorine structure. Since the conversion from prephenic acid into tyrosine in narcissi is probably irreversible, as it is in other systems [72], these results present evidence for the first theory [43].



Haemanthamine *(73)* is also formed from tyrosine via norbelladine *(67)*. This is proved by the fact that after administration of [2-^{14}C]tyrosine and [1-^{14}C]norbelladine, the radioactivity in both cases was detected only in the carbon atom isolated [68, 73] as formaldehyde, as theoretically expected.

However, this clarifies only the origin of rings C and D of the *Amaryllidaceae* alkaloids. In order to investigate the origin of rings A and B, which according to theory should also originate from tyrosine or an equivalent compound, [3-^{14}C]tyrosine was administered to *Sprekelia formosissima*. Radioactive haemanthamine *(73)*, haemanthidine *(76)*, and tazettine *(79)* were then isolated from this plant [74]. If [3-^{14}C]tyrosine is also a precursor of ring A, then the radioactivity should be found in positions 6 and 11 of haemanthidine and haemanthamine, while in tazettine it should be found in the carbon atoms marked with an asterisk and a cross. Degradation of haemanthamine according to the above scheme yielded the



diphenyl derivative *(77)*, the methyl group of which corresponds to C-6; *(77)* was, however, completely inactive. All of the radioactivity was located in the carboxyl group of the glycine derivative, which corresponds to C-11 [74]. Haemanthidine and tazettine were degraded according to a similar scheme. In both cases, contrary to expectations, only C-11 [in *(76)* and *(79)*] was radioactive. This means either that a C_6–C_1-fragment does not constitute a precursor of ring A in these three alkaloids, or that this unit cannot originate from tyrosine in *S. formosissima* [74]. Administration of [3-^{14}C]-tyrosine to *Haemanthus natalensis* led to the same results; *i.e.* radioactive haemanthamine *(73)*, haemanthidine *(76)*, and

[69] *W. C. Wildman, H. M. Fales, R. J. Highet, S. W. Breuer*, and *A. R. Battersby*, Proc. chem. Soc. (London) *1962*, 180.

[70] *A. R. Battersby, R. Binks*, and *W. C. Wildman*, Proc. chem. Soc. (London) *1960*, 410.

[71] *D. H. R. Barton, G. W. Kirby, J. B. Taylor, G. M. Thomas*, Proc. chem. Soc. (London) *1962*, 179.

[72] *I. Schwinck* and *E. Adams*, Biochim. biophysica Acta *56*, 102 (1959); *O. L. Gamborg* and *A. C. Neish*, Canad. J. Biochem. Physiol. *37*, 1277 (1959).

[73] *H. M. Fales* and *W. C. Wildman*, J. Amer. chem. Soc. *82*, 197 (1960).

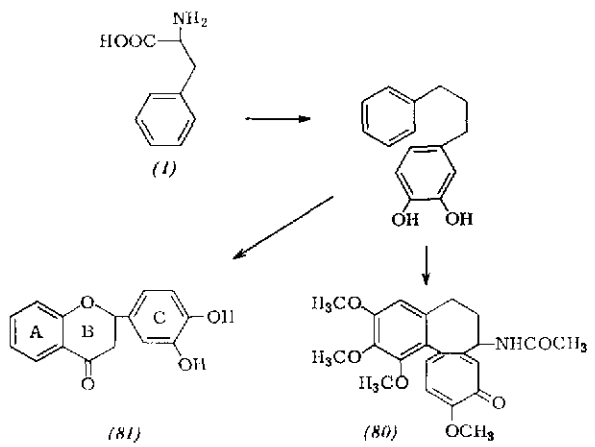
[74] *W. C. Wildman, H. M. Fales*, and *A. R. Battersby*, J. Amer. chem. Soc. *84*, 681 (1962).

6-hydroxycrinamine *(76)* were obtained. Degradation of the haemanthamine also showed that all of the radioactivity was in C-11 [75]. Benzylamine *(78)* was incorporated into galanthamine in King Alfred narcissi [71].

On the other hand, it was shown [76] that [3-^{14}C]phenylalanine is a precursor of ring A and of the benzyl carbon in lycorine *(75)* and belladine *(68)*, but not of rings C and D.

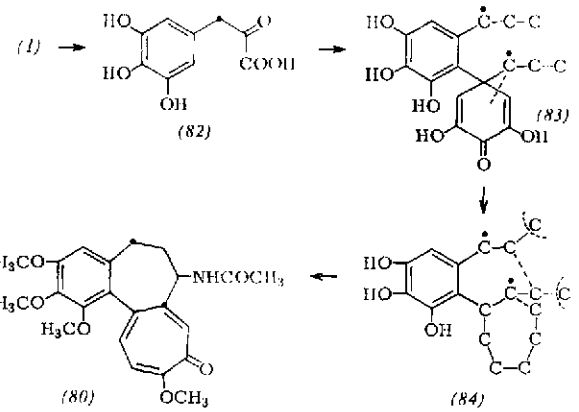
4. Colchicine

Colchicine *(80)*, the alkaloid of meadow saffron (*Colchicum autumnale*), is especially interesting from the biosynthetic point of view because of its tropolone ring and the unusual position of its nitrogen atom. There are several hypotheses for its biogenesis; invariably, phenylalanine or a corresponding compound is supposed to be involved. According to the scheme of *Anet* and *Robinson* [77], colchicine is biogenetically related to the flavones *(81)*. It is known that ring A in flavones is derived from an acetate entity and that the remainder of the molecule is derived from phenylalanine *(1)* [78]. Accordingly, the tropolone ring is supposed to be formed by expansion of the catechol ring by interspersion of a C_1-fragment.

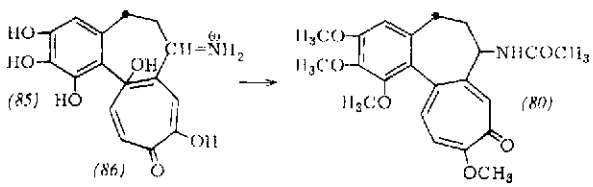


Another hypothesis [79] postulates the formation of colchicine *(80)* by oxidative coupling of two molecules of 3,4,5-trihydroxyphenylpyruvic acid *(82)* to give compound *(83)* and ring expansion of the latter to *(84)*. 3,4,5-Trihydroxyphenylpyruvic acid is related to phenylalanine *(1)*. *Wenkert* [60] assumes that colchicine must originate by condensation of a protonated Schiff base *(85)*, which is formed from prephenic acid *(11)* or phenylalanine *(1)* and 5-hydroxytropolone *(86)*; the latter is assumed to arise from shikimic acid.

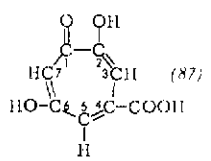
Recently, another hypothesis [80] for the biosynthesis of colchicine has been proposed. This again includes a



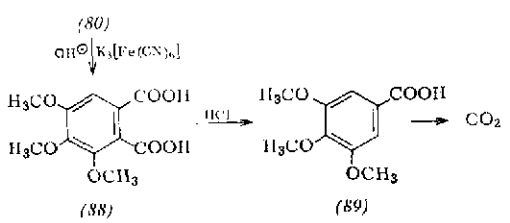
tropolone ring in the synthetic pathway and assumes an oxidative coupling reaction similar to that encountered in the formation of the morphine skeleton or the lycorine and galanthamine system (see also [81]).



The tropolone ring of stipitatic acid [82] (2,6-dihydroxy-2,4,6-cycloheptatrien-1-one-4-carboxylic acid) *(87)* can be partially synthetized by *Penicillium stipitatum* from acetate residues (see also [83]). After administration of [1-^{14}C]acetate, 41 % of the radioactivity is found in C-4 and 56 % in C-6.



It has in fact been shown that [3-^{14}C]phenylalanine is incorporated into colchicine by *Colchicum byzantinum* [81]. Degradation of colchicine via 3,4,5-trimethoxyphthalic acid *(88)* to trimethoxybenzoic acid *(89)* and subsequent decarboxylation show that all of the radioactivity is located in the carbon dioxide.



On the basis of these findings, *Leete* et al. [84] proposed a modified *Anet-Robinson* scheme. According to this scheme, the flavone precursor *(90)* originates from

[75] *P. W. Jeffs*, Proc. chem. Soc. (London) *1962*, 80.

[76] *R. J. Suhadolnik*, *A. G. Fischer*, and *I. Zulalian*, J. Amer. chem. Soc. *84*, 4348 (1962); *W. C. Wildman*, *A. R. Battersby*, and *S. W. Breuer*, J. Amer. chem. Soc. *84*, 4599 (1962).

[77] *F. A. L. v. Anet* and *R. Robinson*, Nature (London) *166*, 924 (1950).

[78] *H. Grisebach*, Z. Naturforsch. *12b*, 227, 597 (1957); *13b*, 335 (1958); *T. A. Geissman* and *T. Swain*, Chem. and Ind. *1957*, 984; *H. Reznik* and *R. Urban*, Naturwissenschaften *44*, 592 (1957); *E. W. Underhill*, *J. E. Watkin*, and *A. C. Neish*, Canad. J. Biochem. Physiol. *35*, 219, 229 (1957).

[79] *B. Belleau*, Experientia *9*, 178 (1953).

[80] *A. I. Scott*, Nature (London) *186*, 556 (1960).

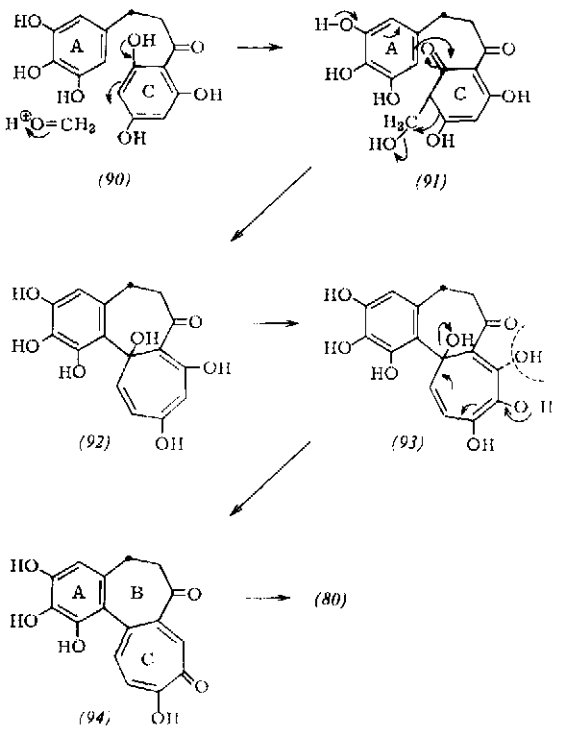
[81] *H. Erdtmann* and *C. A. Wachtmeister* in: Festschrift für A. Stoll. Birkhäuser, Basel 1957. p. 144.

[82] *R. Bentley*, Biochim. biophysica Acta *29*, 666 (1958).

[83] *J. H. Richards* and *L. D. Ferretti*, Biochem. Biophys. Res. Commun. *2*, 107 (1960).

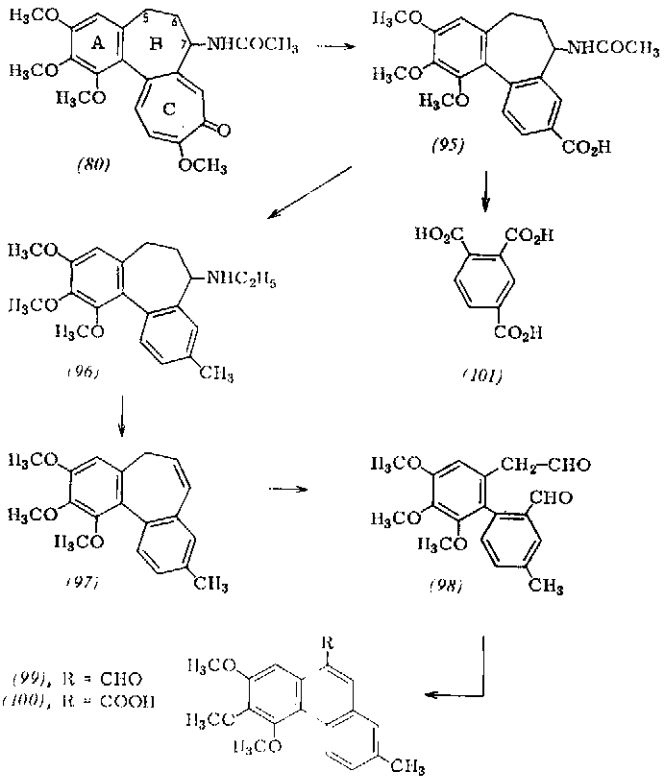
[84] *E. Leete* and *P. E. Nemeth*, J. Amer. chem. Soc. *82*, 6055 (1960).

phenylalanine and acetate residues and then reacts with a C_1-fragment to give compound *(91)*. The latter undergoes expansion of ring C. Subsequent condensation with ring A then leads to the colchicine structure *(92)*. Hydroxylation of the nucleus would yield *(93)*. After elimination of water and loss of a hydroxyl group, *(93)* could yield *(94)*, which after methylation, reductive amination, and acetylation would give colchicine *(80)*. The dot in formulae *(90)* to *(94)* indicates the consecutive positions of the radioactivity from [3-^{14}C]phenylalanine.



[*Me*-^{14}C]Methionine [85,86] is incorporated into colchicine. So is [^{14}C]formate, albeit to a smaller extent. The radioactivity of the methionine is located almost exclusively in the methyl groups; 10 % is found in the *O*-methyl group of the tropolone ring and 90 % in the methoxyl groups of the benzene ring [86].

After administration of [2-^{14}C]tyrosine, the radioactivity would be expected to occur in C-6 by analogy to the incorporation of [3-^{14}C]phenylalanine [85,86]. Degradation [85] of the colchicine *(80)* from this experiment proceeded via *allo*-colchiceine *(95)* and the base *(96)* to a neutral product *(97)*. The resulting glycol was cleaved with lead tetraacetate; the resulting dialdehyde *(98)* was cyclized to the phenanthrene-5-carboxaldehyde *(99)*. The carboxyl group of the corresponding acid *(100)*, which represents the original carbon atom 6, is practically inactive; 50 % of the radioactivity is found in the *N*-acetyl group, 39 % in the remaining phenanthrene residue. The authors of [85] propose a degradation of the aromatic amino acid to a C_6–C_1 compound before its incorporation into colchicine. However, in the synthesis of flavone, the C_6–C_3 nucleus is incorporationed as a whole.



According to available information [82,83] and according to some of the hypotheses mentioned above, [1-^{14}C]-acetate should be incorporated into the tropolone ring; however, it does in fact give rise only to the *N*-acetyl group. The neutral product *(97)* and the trimelitic acid *(101)* resulting from *allo*-colchiceine *(95)* on oxidation were practically inactive [85,86].

These negative results should be interpreted only with great caution, however, as it is questionable whether alkaloids were formed at all in the allotted time. The *N*-acetyl group may simply have become labelled by exchange.

The results obtained up to now do not yield a comprehensive picture of the biosynthesis of colchicine. Much more work is needed before this interesting problem will be solved.

5. Gliotoxin

Gliotoxin *(104)*, an antibiotic formed by several fungi, also belongs to the phenylalanine family from a biogenetic viewpoint. [1-^{14}C]Phenylalanine and [2-^{14}C]-phenylalanine *(1)* are incorporated to a large extent [87], whereas tryptophan and sodium acetate are much less effective precursors. Administration of [1-^{14}C]phenylalanine followed by degradation of the gliotoxin to indole-2-carboxylic acid *(105)* and subsequent decarboxylation yielded carbon dioxide which contained almost all of the radioactivity of the original alkaloid. This indicates that the indole part of gliotoxin is specifically synthetized from this amino acid.

This was confirmed [88] by using uniformly labelled [^{3}H]-phenylalanine, which was incorporated to a great extent. The high degree of incorporation of uniformly labelled [^{3}H]-*m*-tyrosine *(102)* shows that this unusual

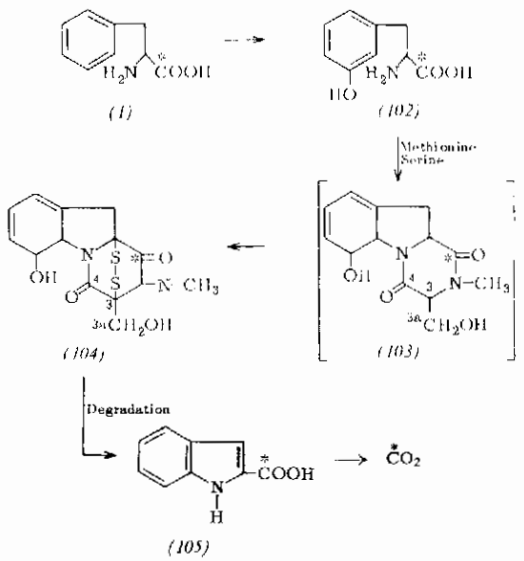
[85] *A. R. Battersby* and *J. J. Reynolds*, Proc. chem. Soc. (London) *1960*, 346.

[86] *E. Leete* and *P. E. Nemeth*, J. Amer. chem. Soc. *83*, 2192 (1961).

[87] *R. J. Suhadolnik* and *R. G. Chenoweth*, J. Amer. chem. Soc. *80*, 4391 (1958).

[88] *J. A. Winstead* and *R. J. Suhadolnik*, J. Amer. chem. Soc. *82*, 1644 (1960).

amino acid can constitute a C_9 intermediate between phenylalanine and gliotoxin. The *N*-methyl group can be derived from methionine or its equivalent (serine and glycine). Degradation of the gliotoxin obtained after administration of [3-^{14}C]serine showed that 19 % of the radioactivity was located in the indole-2-carboxylic acid *(105)* and 25 % in the *N*-methyl group. Hence, 56 % must be distributed among carbon atoms 3, 3a, and 4. In experiments with [1-^{14}C]serine, the indole-2-carboxylic acid and the *N*-methyl groups remained unlabelled, so that here all of the activity must have been located in carbon atoms 3, 3a, and 4. On the basis of these results it can be assumed that serine is a direct precursor for carbon atoms 3, 3a, and 4 of gliotoxin, and that the biosynthesis of gliotoxin *(104)* proceeds from phenylalanine *(1)* via *m*-tyrosine *(102)* and a hypothetical dethiogliotoxin *(103)*, as shown in Scheme 4.

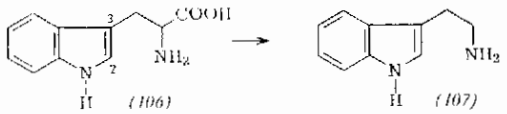


Scheme 4. Biosynthesis and degradation of gliotoxin *(104)*.

Gliotoxin and even more so the hypothetical intermediate *(103)* can be classified as diketopiperazines. Further interesting metabolic products of fungi belong in this group. These include tenuazonic acid [89], aspergillic acid [90], mycelianamide [91], echinuline [92], and L-phenylalanine anhydride [92a].

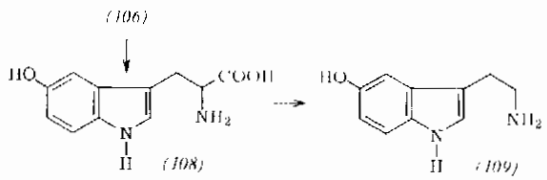
II. Indole Alkaloids

The number of indole alkaloids is just as large as that of the phenylalanine family. However, their biosynthesis has not yet been investigated as intensively as that of the phenylalanine derivatives. It has long been suspected that tryptophan *(106)* is the parent of this large group [20,54]. After decarboxylation, tryptophan is converted into tryptamine *(107)*, which, just like phenethylamine, is capable of undergoing a whole series of condensation reactions.

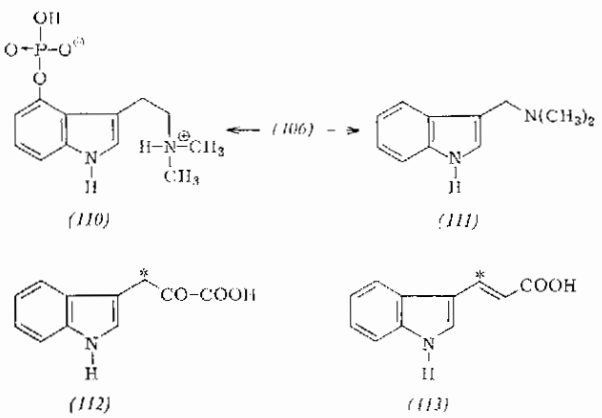


1. Tryptamine Derivatives

Several indolylalkylamines exist, of which the most important is serotonin, 5-hydroxytryptamine *(109)*, which occurs predominantly in animals but also in plants. This amine is produced by hydroxylation of tryptophan *(106)* to 5-hydroxytryptophan *(108)* and subsequent decarboxylation [93]. Tryptamine itself cannot be hydroxylated.



Another tryptamine is psilocyhine *(110)*, the active constituent of the Mexican hallucinogenic fungi of the genus *Psilocybe*. This compound is a phosphoric ester of *N*,*N*-dimethyl-4-hydroxytryptamine. In this case, too, it was shown that labelled tryptophan *(106)* is incorporated into psilocybine; *i.e.* it is possible to oxidize the indole nucleus specifically in the 4-position [94]. This position is of great significance in the synthesis of the lysergic acid skeleton *(143)*.



2. Gramine

Gramine occupies a special position among the indolyl alkylamines. Its aliphatic nitrogen atom is one carbon removed from the indole ring, while that of tryptamine is two carbons away. If [3-^{14}C]tryptophan is adminis-

[89] *C. E. Stickings* and *R. J. Townsend*, Biochem. J. *78*, 412 (1961).

[90] *J. C. McDonald*, J. biol. Chemistry *236*, 512 (1961); *237*, 1977 (1962).

[91] *A. J. Birch*, *R. J. English*, *R. A. Massy-Westropp*, and *H. Smith*, J. chem. Soc. (London) *1958*, 369.

[92] *A. J. Birch*, *G. E. Blance*, *S. David*, and *H. Smith*, J. chem. Soc. (London) *1961*, 3129.

[92a] *I. H. Birkinshaw* and *Y. S. Mohammed*, Biochem. J. *85*, 523 (1962).

[93] *S. Udenfriend*, *C. R. Creveling*, *H. Posner*, *B. G. Redfield*, *J. Daly*, and *B. Witkop*, Arch. Biochem. Biophysics *83*, 501 (1959).

[94] *A. Brack*, *A. Hofmann*, *F. Kalberer*, *H. Knobel*, and *J. Rutschmann*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *294*, 230 (1961).

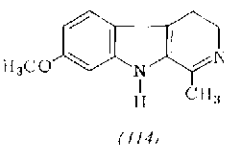
tered to barley seedlings, the gramine isolated is radioactive, and, moreover, is so only at the aliphatic carbon [95]. After administration of [β-$^{14}C_2$]tryptophan, the ratio of radioactivity between these two positions in the gramine is the same as that in the tryptophan administered [96]. This means that in the course of the biosynthesis of gramine *(111)*, the side chain of the tryptophan *(106)* is lapped off to the β-C atom and the indole ring is maintained as a whole. Normal degradation of tryptophan leads to indol-3-ylacetic acid or to indol-3-ylacetaldehyde, and in many microorganisms, to indol-3-ylcarboxaldehyde. Indol-3-ylacetic acid and its amide, as well as indol-3-ylglyoxylic acid and indol-3-ylcarboxaldehyde, were labelled with ^{14}C at the aliphatic carbon atom adjoining the indole ring and tested as biosynthetic precursors; however, in no case was radioactive gramine obtained [97]. The degradation of tryptophan to gramine must therefore proceed by way of other intermediates. On the other hand, [β-^{14}C]indol-3-ylpyruvic acid *(112)* and [β-^{14}C]indol-3-ylacrylic acid *(113)* were incorporated specifically into gramine when administered to whole plants [97].

In other experiments [98], [β-^{14}C]indol-3-ylacrylic acid, tryptamine, indol-3-ylacetonitrile, indol-3-ylacetaldehyde, and indol-3-yl-lactic acid showed little or no incorporation when administered to sliced barley sprouts. Some compounds that have proved to be precursors of tryptophan in bacteria [99], *e.g.*, shikimic acid, anthranilic acid, indole, and serine, may also be precursors of gramine in barley [98]. The methyl groups of gramine are derived from methionine [100]. After administration of a mixture of [β-^{14}C]-DL-tryptophan and [β-^{3}H]-DL-tryptophan the gramine formed was radioactive only in the methylene group of the side-chain. In addition, the ratio ^{14}C:^{3}H was the same in gramine as it had been in the tryptophan mixture, which shows that the methylene group of tryptophan remains intact during the synthesis of gramine [100a].

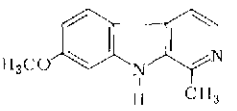
3. Carboline Derivatives

Tryptamine can be condensed to carboline derivatives, *e.g.* tetrahydroharman *(117)*, just as phenethylamine derivatives can condense with aldehydes or other carbonyl compounds. Tetrahydroharman is the parent substance of the harmala alkaloids harmaline *(114)*, harmine *(115)*, and harman *(116)*, obtained from *Peganum harmala*.

Under physiological conditions (25 °C and pH 5–6), tetrahydroharman *(117)* can be produced in good yield from tryptamine *(107)* and acetaldehyde [19, 24, 101].



(114)



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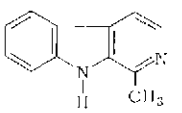

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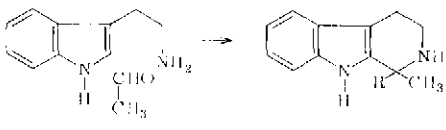
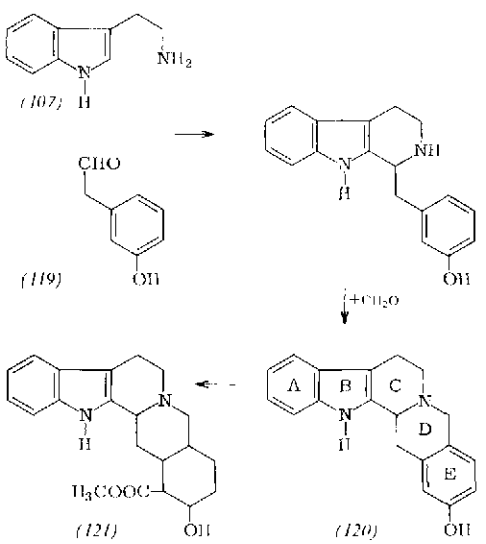


(107) *(117)*, R = H
(118), R = CO_2H

Under these conditions, tryptamine also condenses readily with enolic α-keto acids to yield tetrahydro-4-carboline-1-carboxylic acids; *e.g.* pyruvate yields *(118)* [102]. Using labelled tryptophan, it was shown that this amino acid is indeed a precursor of the carbolines in *Peganum harmala* [103].

4. Yohimbine, Cinchonine, and Strychnine

Alkaloids of the yohimbine type *(121)* are somewhat similar to the berberines, except that tryptamine *(107)* replaces the phenethylamine. It was long suspected [20, 54, 104] that the ring system *(120)* can be formed by condensation of *m*-hydroxyphenylacetaldehyde *(119)* with tryptamine *(107)*, followed by a second condensation with formaldehyde. However, ring E would then be aromatic, whereas it is alicyclic in yohimbine



(107) *(119)* *(121)* *(120)*

[95] *K. Bowden* and *L. Marion*, Canad. J. Chem. *29*, 1037, 1045 (1951).

[96] *E. Leete* and *L. Marion*, Canad. J. Chem. *31*, 1195 (1953).

[97] *A. Breccia* and *L. Marion*, Canad. J. Chem. *37*, 1066 (1959).

[98] *F. Wightman*, *M. D. Chisholm*, and *A. C. Neish*, Phytochemistry *1*, 30 (1961).

[99] *B. D. Davis*, Adv. Enzymol. *16*, 247 (1955); Arch. Biochem. Biophysics *78*, 497 (1958); *C. Yanofsky*, Biochim. biophysica Acta *20*, 438 (1956); *C. Yanofsky* and *M. Rachmeler*, ibid. *28*, 640 (1958); *O. H. Smith* and *C. Yanofsky*, J. biol. Chemistry *235*, 2051 (1960).

[100] *S. H. Mudd*, Biochim. biophysica Acta *37*, 164 (1960).

[100a] *D. O'Donovan* and *E. Leete*, J. Amer. chem. Soc. *85*, 461 (1963).

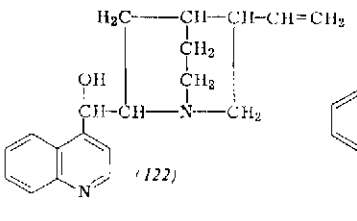
[101] *G. Hahn* and *H. Ludewig*, Ber. dtsch. chem. Ges. *67*, 2031 (1934).

[102] *G. Hahn*, *L. Bärwald*, *O. Scholes*, and *H. Werner*, Liebigs Ann. Chem. *520*, 107 (1935); *G. Hahn* and *A. Hansel*, Ber. dtsch. chem. Ges. *71*, 2163 (1938).

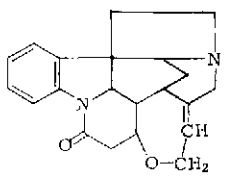
[103] *D. Gröger* and *H. Simon*, Lecture, 2. Alkaloidtagung, Halle (Germany) 1960.

[104] *G. Barger* and *C. Scholz*, Helv. chim. Acta *16*, 1343 (1933); *G. Hahn* and *H. Ludewig*, Ber. dtsch. chem. Ges. *67*, 203 (1934); *G. Hahn* and *H. Werner*, Liebigs Ann. Chem. *520*, 123 (1935).

(121). For this reason it has also been suggested that rings D and E may arise from prephenic acid *(11)* [105] or cyclopentanomonoterpenes [106]. Cinchonine *(122)* and strychnine *(123)* are also thought to be formed along the pathway postulated by the first hypothesis. The phenylacetaldehyde component is supposed to condense with tryptamine *(107)* at the 2-position of its indole ring to form yohimbine *(121)*, whereas in the biogenesis of strychnine *(123)*, this would occur at the 3-position *(124)*, giving rise to indolenine *(125)*. Condensation with formaldehyde would lead to the pentacyclic structure *(126)*, which would be capable of further

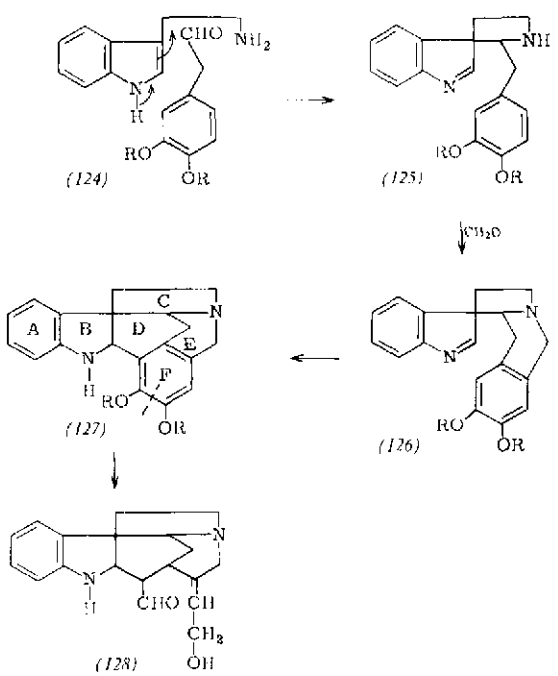


(122)



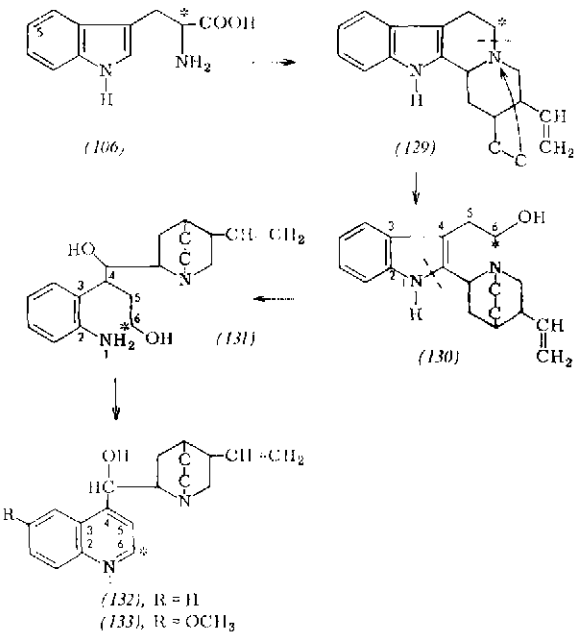
(123)

condensation, resulting in *(127)*. If it is also assumed that ring F (derived from phenylalanine) is cleaved along the dotted line in *(127)*, then it is easy to establish a structural relationship between compound *(128)* and strychnine by adding a molecule of acetate. This ring cleavage, named after *Woodward* [54, 107], has played a major role in all theories dealing with the biogenesis of alkaloids. For example, the biosyntheses of quinine *(133)* and ajmaline *(134)* [54] are thought to involve a Woodward cleavage. In the case of cinchonine *(122)*, an alkaloid with the same carbon skeleton as quinine *(133)*, it is assumed that compound *(129)*, which results from Woodward cleavage of compound *(120)*, undergoes further cleavage and ring coupling to yield cinchonamine *(130)*. The latter is thought to undergo a third



(124) *(125)* *(126)* *(127)* *(128)*

Woodward cleavage to give *(131)* and further ring closure to yield the skeleton of cinchonine *(132)* or quinine *(133)*. The methoxyl group in quinine corresponds to C-5 in tryptophan; quinine is thus substituted in the same position as serotonin *(109)*. Although there is still no experimental evidence for these hypotheses concerning the biosynthesis of yohimbine *(121)* and strychnine *(123)*, it has been tested for quinine *(133)* with labelled tryptophan *(106)*. [β-^{14}C]Tryptophan is in fact incorporated into quinine *(133)* by *Chinchona succirubra* [the position of the label is indicated with an asterisk in

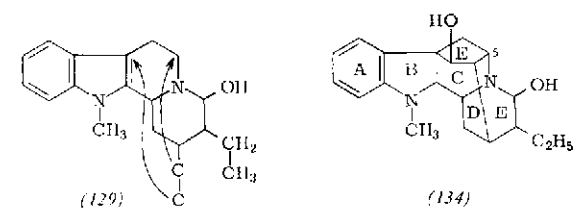


(106) *(129)* *(130)* *(131)* *(132)*, R = H *(133)*, R = OCH_3

formula *(106)*]. After degradation, all of the radioactivity was found in C-6, just as expected by theory [108]. Whether the quinuclidine ring really does originate from phenylalanine has not yet been determined.

5. Ajmaline, Serpentine, and Reserpine

Ajmaline is also thought to be derived biogenetically from the yohimbine skeleton *(121)* [54]. The hypothesis postulated for the biogenesis of this alkaloid has contributed materially to the clarification of its structure. The product of Woodward cleavage *(129)* is thought to form two new rings with one of the unattached C_2-fragments, giving rise to ajmaline *(134)*.



(129) *(134)*

[2-^{14}C]Tryptophan has been found to be incorporated by *Rauwolfia serpentina* into ajmaline *(134)*, serpentine *(135)*, and reserpine *(136)* [109]. Systematic degrada-

[105] *E. Wenkert, N. V. Bringi*, J. Amer. chem. Soc. *81*, 1474 (1959).

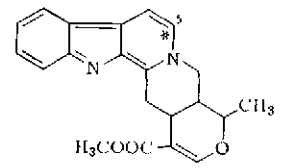
[106] *R. Thomas*, Tetrahedron Letters *1961*, 544.

[107] *R. B. Woodward*, Nature (London) *162*, 155 (1948).

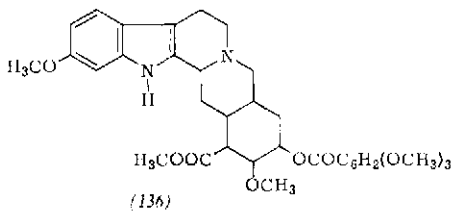
[108] *N. Kowanko* and *E. Leete*, J. Amer. chem. Soc. *84*, 4919 (1962).

[109] *E. Leete*, Chem. and Ind. *1960*, 692; J. Amer. chem. Soc. *82*, 6338 (1960).

tion of the ajmaline [109] and serpentine [110] showed that the radioactivity is localized in C-5, as expected by theory. The degradation [109,110] proceeded via *N*(1)-methylharman *(137)*, which after reduction, Hofmann degradation, and another reduction yielded the base *(138)*. Further Hofmann degradation led to 1-methyl-2-ethyl-3-vinylindole *(139)*, which was cleaved with osmium tetroxide and periodate via the corresponding

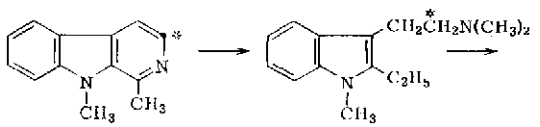


(135)

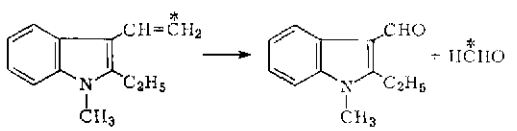


(136)

glycol to yield 1-methyl-2-ethylindol-3-ylcarboxaldehyde *(140)* and formaldehyde. The formaldehyde corresponded to C-5 and contained all of the radioactivity of the ajmaline and the serpentine. After hydrolysis of reserpine *(136)*, only the reserpinic acid – the heterocyclic yohimbine system [110] – was found to be radioactive. Following administration of [^{14}C]formate, only 12 % of the radioactivity was found in C-21 and 48 % in the *N*-methyl group of ajmaline [111]. The remainder was not analyzed.

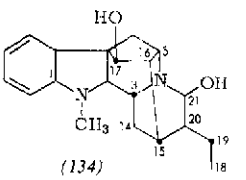


(137) *(138)*

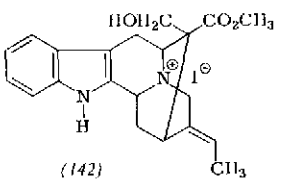


(139) *(140)*

According to one hypothesis, rings D, E, and F of ajmaline *(134)* were supposed to result from a hydroxylated phenylalanine via the yohimbine structure, which by Woodward cleavage *(129)* and another ring closure would form ajmaline *(134)*. However, [2-^{14}C]phenylalanine was incorporated into ajmaline either not at all or only in insignificant amounts [112], so that this amino acid can be excluded as a precursor. According to another hypothesis [60,105,110], these carbon atoms were thought to originate from prephenic acid *(11)* and subsequent Woodward cleavage. However, when [2-^{14}C]-alanine, which is closely related to prephenic acid through pyruvic acid [113], was administered, it was incorporated in only insignificant quantities, merely 2 % of the radioactivity being recovered as postulated in position 3 [112]. Hence, this hypothesis can also be discarded. Use of [2-^{14}C]mevalonic acid, a proved precursor of terpenes [114], yielded inactive ajmaline [112]; this makes another hypothesis [115,116] unlikely whereby the ring in question was supposed to be formed from a monoterpene of type *(141)*, by cleavage at the dotted line. An additional argument against the monoterpene theory is the specific degradation of ajmaline *(134)* intensively labelled by [1-^{14}C]acetate incorporation; here carbon atoms 3 and 19 each contained one-fourth of the activity of the ajmaline, whereas carbon atoms 14 and 18 were inactive [112]. According to the monoterpene theory, the activity should have been distributed as indicated by the asterisks in formula *(141)*. If it is assumed that the remaining half of the radioactivity is in carbon atoms 15 and 17, this would support a theory [112,117] which postulates that the carbon chain 18-19-20-15-14-3 originates by condensation of three molecules of acetyl-coenzyme A; C-18 is then the methyl end of the chain. It is possible that acetyl-coenzyme A is converted into malonyl-coenzyme A before condensation occurs [118]. If C-21 is derived from a C_1-fragment [111], the condensation would have to occur at a methylene group of the poly-β-keto acid. A further condensation with a methylene carbon atom of malonyl-coenzyme A is thought to occur at C-15; a carboxyl group would then have to be eliminated at C-16 in order to give ajmaline, whereas it would be preserved in other alkaloids, *e.g.* macusine A *(142)* [119].



(134) *(141)*



(142)

6. Ergot Alkaloids

All of the ergot alkaloids are also tryptophan derivatives, insofar as they can be derived from the ergoline system *(143)*. *Weygand* and *Floss* [120] have recently reviewed the biosynthesis of this group very extensively (see also [121]). We shall mention only that the ergoline system can be formed by condensation of tryptophan *(106)* with a terpene precursor, *e.g.* mevalonic acid

[110] *E. Leete*, Tetrahedron Letters *1961*, 35.

[111] *P. N. Edwards* and *E. Leete*, Chem. and Ind. *1961*, 1666.

[112] *E. Leete, S. Ghosal*, and *P. W. Edwards*, J. Amer. chem. Soc. *84*, 1068 (1962).

[113] *J. G. Levin* and *D. P. Springson*, Biochem. biophys. Res. Commun. *3*, 157 (1960).

[114] *A. J. Birch, D. Boulter, R. I. Fryer, P. J. Thomson*, and *L. J. Willis*, Tetrahedron Letters *1959*, No. 3, 1.

[115] *E. Wenkert*, J. Amer. chem. Soc. *84*, 98 (1962).

[116] *R. Thomas*, Tetrahedron Letters *1961*, 544.

[117] *E. Schlittler* and *W. I. Taylor*, Experientia *16*, 244 (1960).

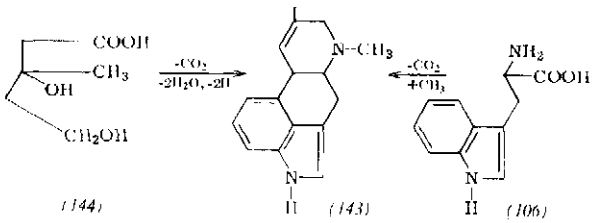
[118] *S. J. Wakil* and *J. Ganguly*, J. Amer. chem. Soc. *81*, 2597 (1959); *R. Bentley, J. G. Keil*, and *D. S. Bhate*, J. Amer. chem. Soc. *83*, 3716 (1961); *R. Bentley* and *J. G. Keil*, Proc. chem. Soc. (London) *1961*, 111; *A. J. Birch, A. Cassera*, and *R. W. Richards*, Chem. and Ind. *1961*, 792.

[119] *A. T. McPhail, J. M. Robertson, G. A. Sim, A. R. Battersby, H. F. Hodson*, and *D. A. Yeowell*, Proc. chem. Soc. (London) *1961*, 223.

[120] *F. Weygand* and *H. G. Floss*, Angew. Chem. internat. Edit. *2*, 243 (1963).

[121] *K. Winkler* and *D. Gröger*, Pharmazie *17*, 658 (1962).

(144). The very high specific degree of incorporation obtained thereby indicates that these experiments approach very closely to what happens *in vivo*.



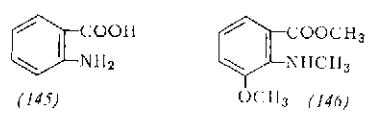
(144) *(143)* *(106)*

III. Anthranilic Acid Family

Besides the simple derivatives of anthranilic acid *(145)*, such as damascenine *(146)*, this group comprises several quinoline and quinazoline alkaloids. No clear separation between these classes of compounds is possible from a chemical viewpoint, as is shown by the fact that the biosynthesis of the quinoline alkaloid quinine *(133)* is also classified under the indole alkaloids.

1. Damascenine

Damascenine *(146)* is methyl 3-methoxy-*N*-methylanthranilate.



(145) *(146)*

However, it has been found that labelled anthranilic acid *(145)* and 3-hydroxyanthranilic acid are incorporated into damascenine in only slight amounts [122, 123]. After administration of [*Me*-^{14}C]methionine, the radioactivity was found only in the three methyl groups of damascenine [123].

2. Quinoline and Quinazoline Alkaloids

Syntheses of quinoline and quinazoline alkaloids under physiological conditions have also been carried out. However, *o*-aminobenzaldehyde *(147)* was used instead of anthranilic acid *(145)* [19].

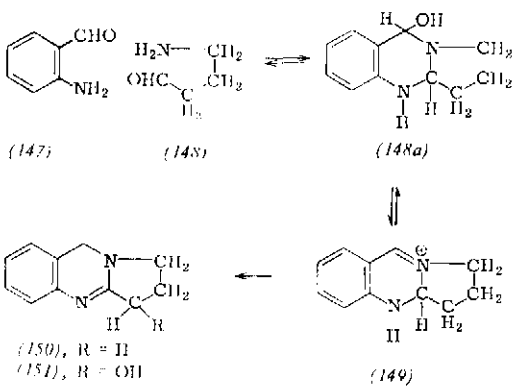
If, for example, *o*-aminobenzaldehyde *(147)* is treated in aqueous solution at pH 5 with the diethylacetal of γ-aminobutyraldehyde *(148)*, which is readily saponified at this pH value, the quaternary base *(149)* is formed in good yield by reversible formation of an aldehyde-ammonia via base *(148a)*. Deoxyvasicine *(150)* can originate from compound *(149)* by prototropy [124].

[122] *M. L. Vishin, K. Mothes, L. Engelbrecht*, and *H.-B. Schröter*, Nature (London) *188*, 61 (1960).

[123] *D. Munsche, H.-B. Schröter*, and *K. Mothes*, Lecture, 2nd International Symposion on the Chemistry of Natural Products, Prague 1962.

[124] *Cl. Schöpf* and *F. Oechler*, Liebigs Ann. Chem. *523*, 1 (1936).

Vasicine *(151)*, also known as peganine, is an alkaloid obtained from *Peganum harmala*. Using [*carboxy*-^{14}C]-anthranilic acid, it has been shown that this amino acid is incorporated into peganine by *Peganum harmala* [125]. Either putrescine or proline can be considered as the second precursor. Thus, either deoxyvasicine is formed first and is subsequently oxidized to vasicine, or the precursor is already oxidized. Studies of this are currently in progress.

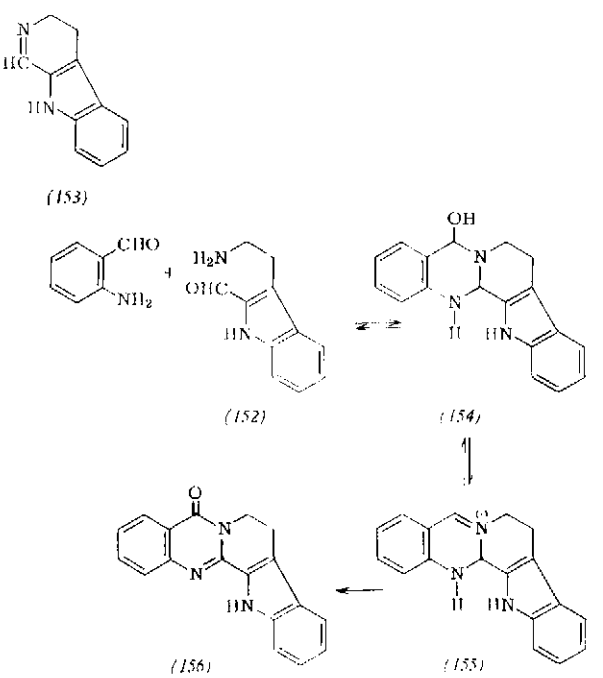


(147) *(148)* *(148a)*

(150), R = H
(151), R = OH

(149)

If the amino aldehyde *(152)*, which is stable in the form of dihydronorharman *(153)*, is used in place of the γ-aminobutyraldehyde *(148)*, the base *(155)* is formed under physiological conditions. The reaction is reversible and proceeds via the addition product *(154)*. The base may be easily oxidized to rutaecarpine *(156)* [19].



(153)

(152) *(154)*

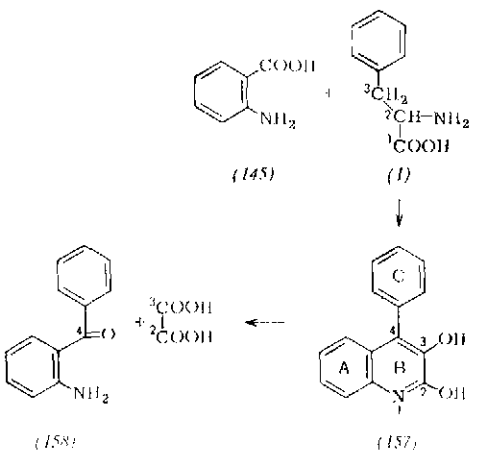
(156) *(155)*

As far as the quinoline alkaloids are concerned, only a few investigations of their biosynthesis *in vivo* have been carried out.

One of the few quinoline compounds about whose biosynthesis some information is available is viridicatine, 2,3-dihydroxy-4-phenylquinoline *(157)*, which can be

[125] *D. Gröger* and *K. Mothes*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *293*, 1049 (1960).

isolated from the mycelium of *Penicillium viridicatum*. A variety of labelled potential precursors have been used in the study of this biosynthesis. The distribution of activity in the resulting viridicatine was investigated by degradation to 2-aminobenzophenone *(158)* and oxalic acid or carbon dioxide [126]. Tritium-labelled anthranilic acid *(145)* was incorporated into viridicatine *(157)* to a moderate extent. However, [carboxy-^{14}C]anthranilic acid was very poorly incorporated. This result can



Scheme 5. Biosynthesis and degradation of viridicatine *(157)*.

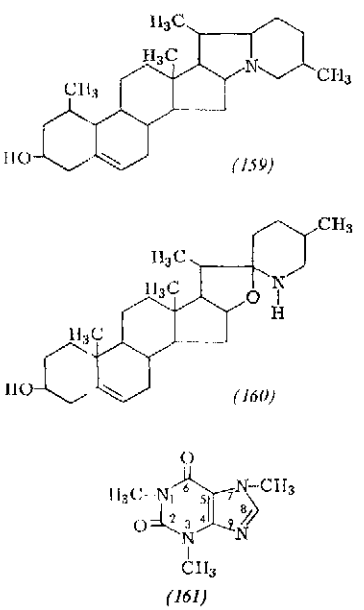
be understood in terms of the mode of biosynthesis shown in Scheme 5. According to this scheme, the carboxyl group of the anthranilic acid is split off during the formation of viridicatine. Moreover, in accordance with Scheme 5, uniformly labelled [^{14}C]phenylalanine, [2-^{14}C]phenylalanine, and [3-^{14}C]phenylalanine were incorporated to a high degree (about 80 %). Degradation according to Scheme 5 following the incorporation of the uniformly labelled phenylalanine showed that 79.4 % of the radioactivity was located in the 2-aminobenzophenone *(158)* and 18.8 % in the carbon dioxide corresponding to the oxalic acid (carbon atoms 2 and 3 of the quinoline chain). If the radioactivity of the uniformly labelled phenylalanine were distributed equally over all of its carbon atoms, a distribution of 77.8 % and 22.2 % would be expected in the products. After administration of [2-^{14}C]phenylalanine, the products of degradation of viridicatine *(157)* yielded all of the radioactivity in the carbon dioxide derived via oxalate (probably C-3), while after administration of [3-^{14}C]phenylalanine all of the radioactivity was in the benzophenone *(158)*. [2-^{14}C]Phenylserine was incorporated to a much smaller extent than phenylalanine. These results indicate that the entire phenylalanine skeleton is incorporated into the viridicatine and that phenylserine is not on the normal biosynthetic pathway. Possibly it is first converted into phenylalanine. The relatively low degree of incorporation of anthranilic acid can be interpreted as an indication that an active precursor rather than anthranilic acid itself is utilized. In any case, the carboxyl group or a corresponding carbon atom is split off during the synthesis of viridicatine. The quinoline ring system of the viridicatine therefore arises in a manner similar to the indole ring system of tryptophan [127].

[126] *M. Luckner* and *K. Mothes*, Tetrahedron Letters *1962*, 1035; Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *296*, 18 (1963).

IV. Miscellaneous

The carbon skeleton of the steroid alkaloids of *Solanum* species appears to originate in a manner similar to that of the animal steroids. This is indicated by successful incorporation experiments with [1-^{14}C]acetate in tomato plants and with [2-^{14}C]acetate and [2-^{14}C]mevalonic acid in *Solanum tuberosum* and *S. aviculare*. In the first experiment, radioactive tomatidine *(160)* [128] was obtained; in the second experiment, radioactive solanidine *(159)* and chaconine were formed [129].

The biosynthesis of the purine alkaloid caffeine *(161)* proceeds in *Coffea arabica* in a manner similar to the synthesis of purines in animals and microorganisms [130]. [3-^{14}C]Serine, [2^{14}C]glycine, [^{14}C]formaldehyde, [^{14}C]formate, and [^{14}C]methanol are all incorporated either in the form of C_1-fragments or as C_1-fragment donors, the incorporation taking place predominantly at carbon atoms 2 and 8. In addition, they also



[127] *J. F. Nyc, H. K. Mitchell, E. Leifer*, and *W. H. Langham*, J. biol. Chemistry *179*, 783 (1949); *D. M. Bonner* and *C. W. H. Partridge*, Fed. Proc. *9*, 154 (1950); *C. W. H. Partridge, D. M. Bonner* and *C. Yanofsky*, J. biol. Chemistry *194*, 269 (1952); *C. Yanofsky*, Biochim. biophysica Acta *16*, 594 (1955); J. biol. Chemistry *223*, 171 (1956); Biochim. biophysica Acta *20*, 438 (1956); *F. W. E. Gibson, C. H. Doy*, and *S. B. Segall*, Nature (London) *181*, 549 (1958); *C. H. Doy* and *F. Gibson*, Biochem. J. *72*, 586 (1959); *O. H. Smith* and *C. Yanofsky*, J. biol. Chemistry *235*, 2051 (1960); *C. H. Doy, A. Rivera*, and *P. R. Srinivasan*, Biochem. Biophys. Res. Commun. *4*, 83 (1961); *C. H. Doy, P. R. Srinivasan*, and *A. Rivera*, Fed. Proc. *20*, 10 (1961).

[128] *H. Sander* and *H. Grisebach*, Z. Naturforsch. *13b*, 755 (1958).

[129] *A. R. Guseva* and *V. A. Paseshnichenko*, Biochem. Russ. *23*, 412 (1958); *A. R. Guseva, M. G. Borikhina*, and *V. A. Paseshnichenko*, ibid. *25*, 282 (1960); *A. R. Guseva, V. A. Paseshnichenko*, and *M. G. Borikhina*, ibid. *26*, 723 (1961).

[130] *L. Anderson* and *M. Gibbs*, Fed. Proc. *20*, 374 (1961); J. biol. Chemistry *237*, 1941 (1962).

enter the *N*-methyl group, as does the methyl group of [*Me*-^{14}C]methionine. It was shown in experiments conducted in the dark that radioactivity from $^{14}CO_2$ occurs mainly in C-6. Carbon atoms 4 and 5 are derived from glycine. In contrast to experiments with tobacco [131], it was shown that [2-^{14}C]glycolic acid is not a methyl donor.

Experiments with green tea leaves have shown that [^{14}C]methylamine is incorporated into caffeine in large amounts, [2-^{14}C]glycine in lesser amounts, and [^{14}C]-urea not at all [132]. No degradation experiments were carried out to determine how the activity is distributed.

V. Summary

The two parts of this review have considered only the most important examples to illustrate current hypotheses of alkaloid biosynthesis and are therefore necessarily incomplete. Nevertheless, the information presented should suffice to show that in no more than the past six years, this complex of problems, which until recently was still only the object of speculation, has been attacked successfully on a broad front. It is certain that further investigations will reveal other entirely new reactions. Yet with the data available, because they have been obtained from work with very different types of alkaloids, some general conclusions are possible. In this we shall exclude the purine alkaloids, which are simple methylation products of oxidized purines.

Although, with the exception of nicotinic acid [133], the origin of the heterocyclic nitrogen has scarcely been studied, it appears on the basis of the widely demonstrated specific incorporation of carbon atoms derived from administered amino acids that alkaloid synthesis is a special case of amino acid metabolism. This is also true for the cases in which nicotinic acid is a constituent unit of the alkaloid, since nicotinic acid itself may be traced back to a proteinogenic amino acid. Anthranilic acid, the synthesis of which is closely coupled with tryptophan metabolism, also falls into this category.

There is as yet no proof that heterocyclically bound alkaloid nitrogen can arise directly from ammonia or its most widespread "detoxified" form, glutamine (again disregarding the case of purines).

In addition to the carbon chains which arise from the amino acids, other carbon atoms can be incorporated, *e.g.* C_1-fragments by participation of the folic acid system, as in the case of narcotine. Other examples include acetyl and malonyl residues as well as mevalonic acid fragments, which can be incorporated in accordance with the general rules of acetyl-CoA biochemistry. The *N*- and the phenolic *O*-methyl groups and occasionally perhaps also *C*-methyl groups, arise mostly from methionine, which in turn is methylated via the folic acid C_1-fragment system.

Ring closure with the participation of the nitrogen can proceed either intramolecularly or intermolecularly.

The diamines are of great significance in intramolecular ring closure; they acquire an aldehyde group in place of an amino group by oxidation and thus are converted into Schiff bases, often spontaneously.

In intermolecular ring closure, derivatives of two of the same (benzylisoquinolines) or of two different (*Vinca* alkaloids) amino acids may be involved.

In all of these cases the condensation proceeds preponderantly by a mechanism whereby one amino acid becomes reactive by decarboxylation to an amine and the other by oxidative deamination to an aldehyde or ketone. Less frequently, amide-type condensations are involved (aspergillic acid, peganine, viridicatine).

Although not yet proved, it is probable that methylation or acetylation takes place before ring closure, thereby blocking other reaction routes.

Formation of additional rings by condensation with C_1-fragments, by Woodward cleavage, and by dehydrogenative coupling of different rings of the same molecule complicate the simple scheme outlined above. Moreover, even that simple scheme has a number of particular unsolved problems, for example the reactivity of relatively inactive carbons, *e.g.* C-4 of the indole ring in the ergoline system.

We must not forget that at the moment the main interest lies in the clarification of the major formal relationships between alkaloids and their percursors and that in most instances the difficult problems of the details of the reaction mechanisms have not even been broached.

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German version: Angew. Chem. *75*, 357 (1963).

[131] *R. U. Byerrum, L. J. Dewey, R. L. Hamill*, and *Ch. D. Ball*, J. biol. Chemistry *219*, 345 (1956).

[132] *G. P. Serenkov* and *E. Projsser*, Dokl. Akad. Nauk S.S.S.R. *140*, 716 (1961).

[133] *E. Mothes, D. Gross, H. R. Schütte*, and *K. Mothes*, Naturwissenschaften *48*, 623 (1961); *D. Gross, H. R. Schütte, G. Hübner*, and *K. Mothes*, Tetrahedron Letters *1963*, 541.

Syntheses of Heterocyclic Compounds from Aminoguanidine

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Due to its unique structure, aminoguanidine is capable of reacting as a derivative of hydrazine, guanidine or formamidine. Addition and condensation reactions yield products which can be cyclized to heterocyclic compounds. Frequently, heterocyclics are directly accessible from aminoguanidine in one stage.

Introduction

A. Pyrazoles
- I. Synthesis of pyrazole derivatives
- II. The chemistry of 1-guanylpyrazoles
  1. Hydrazinolysis
  2. Aminolysis
  3. Azidolysis
  4. Mechanism of deguanylation
  5. Halogenation
- III. Synthesis of pyrazolones
- IV. Synthesis of pyrazolines

B. 1,2,4-Triazoles
- I. Cyclization of acylaminoguanidines
  1. Acylation of aminoguanidine with aliphatic acids
  2. Acylation of nitroaminoguanidine
  3. Acylation of aminoguanidine with aromatic acids and their derivatives
  4. Reduction of nitroguanidines in the presence of acids
  5. Aminolysis of acyl-*S*-alkylisothiosemicarbazides
  6. Synthesis of acylaminoguanidines from acylhydrazines
- II. Cyclization of aminoguanyl(thio)ureas and guanylthiosemicarbazides
- III. Synthesis of triazoles from biguanidines
- IV. Synthesis of triazoles from biguanides
- V. Synthesis of triazoles from *s*-triazine
- VI. Other syntheses of triazoles

C. Thiadiazoles

D. Tetrazoles
- I. Reaction between aminoguanidine and nitrous acid
  1. Reaction in neutral or weakly acidic solution
  2. Dyes from diazotized aminoguanidine
  3. Reaction in strongly acidic solution: guanyl azide
  4. Reactions of guanyl azides
     a) Conversion of guanyl azide into guanidine or aminoguanidine derivatives
     b) Cyclization of guanyl azide to tetrazoles
     c) Cyclization of guanyl azide derivatives containing electronegative substituents
        α) Reaction of 1,3-diaminoguanidine with nitrous acid
        β) Nitroguanyl azide
- II. Synthesis of tetrazoles from aminoguanidine *via* formazans
- III. Other syntheses of tetrazoles

E. Pyrimidines

F. 1,2,4-Triazines
- I. Synthesis of 1,2,4-triazines from aminoguanidine
  1. With halogenated carbonyl compounds
  2. With dicarbonyl compounds
  3. With quinones
- II. Synthesis of 1,2,4-triazines from diaminoguanidine

G. Tetrazines

H. Eight-membered Heterocyclics

Introduction

Ever since the discovery of the parent compound in 1892 by *Thiele* [1], the chemistry of aminoguanidine and related compounds has been a fruitful field of research and has yielded interesting results from both the theoretical and practical points of view. The particular usefulness of aminoguanidine for the synthesis of heterocyclics had become obvious very early as a result of the fundamental investigations of *Thiele* and his collaborators.

A comprehensive survey by *Lieber* and *Smith* [2] provides an excellent summary of aminoguanidine chemistry up to 1938. Since then, the field has expanded rapidly. Much progress has been recorded in the synthesis of aminoguanidine and its derivatives, both by consolidation of the existing methods and by the discovery of new reactions. This aspect of the subject has been reviewed by us recently [3].

Even more significant and extensive research projects applied aminoguanidine derivatives for synthetizing heterocyclics. The presence in the aminoguanidine structure of a chain of three nitrogen and one carbon atoms makes this compound a versatile starting material for a wide variety of cyclizations. The present survey attempts to review the advances in the use of aminoguanidine in heterocyclic chemistry during the past twenty-five years. The material is dealt with in the order of increasing ring complexity of the resulting heterocyclic systems.

A. Pyrazoles

I. Synthesis of Pyrazole Derivatives

Condensation of aminoguanidine *(1)* with β-diketones, such as acetylacetone *(2)*, is a well established synthesis of 3,5-dialkyl-1-guanylpyrazoles *(3)* [4]. By this general

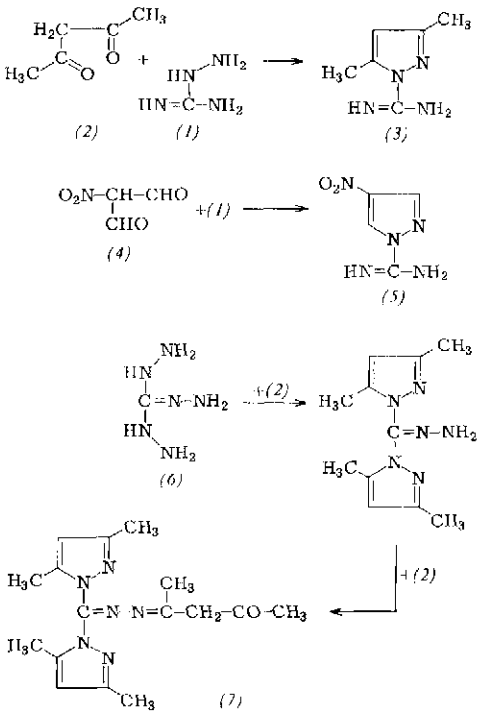
[1] *J. Thiele*, Liebigs Ann. Chem. *270*, 1 (1892).

[2] *E. Lieber* and *G. B. L. Smith*, Chem. Reviews *25*, 213 (1939).

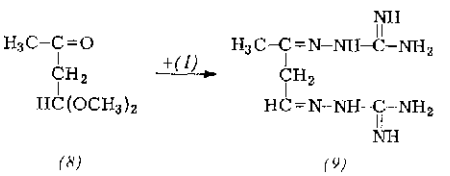
[3] *F. Kurzer* and *L. E. A. Godfrey*, Chem. and Ind. *1962*, 1584.

[4] *J. Thiele* and *E. Dralle*, Liebigs Ann. Chem. *302*, 275 (1898).

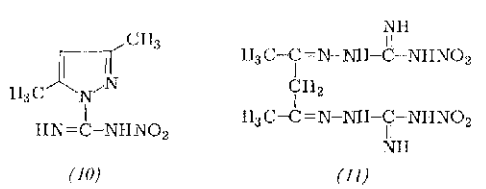
method, nitromalondialdehyde *(4)* yields 1-guanyl-4-nitropyrazole *(5)* [5], and 3 moles of acetylacetone *(2)* react similarly with 1,2,3-triaminoguanidine *(6)* to yield 1,1-bis-(3,5-dimethylpyrazol-1-yl)-4-methyl-2,3-diaza-1,3-heptadien-6-one *(7)* as main product [6]. The corresponding reaction of diaminoguanidine has apparently not yet been studied.



In contrast to the general ready formation of pyrazoles from acetylacetone and aminoguanidine, *Burness* [7] found that 4,4-dimethoxy-2-butanone *(8)* reacts with one or two moles of aminoguanidine sulfate *(1)* to give merely butane-1,3-dione bis(guanylhydrazone) *(9)*, which could not be cyclized to a pyrazole by any of the usual methods.



3,5-Dimethyl-1-nitroguanylpyrazole *(10)* has recently been obtained similarly from 3-nitro-1-aminoguanidine [8, 9]. A certain amount of osazone *(11)* is also formed. In general, the relative proportions of hydrazone and pyrazole formed in the reaction between acylhydrazides and β-diketones depend on the electrophilic nature of the acyl group of the hydrazide involved [9, 10].



[5] *F. L. Scott* and *J. Reilly*, Chem. and Ind. *1952*, 907.

[6] *F. L. Scott, M. Cashman*, and *J. Reilly*, J. Amer. chem. Soc. *75*, 1510 (1953).

[7] *D. M. Burness*, J. org. Chemistry *21*, 97 (1956).

[8] *R. A. Henry* and *G. B. L. Smith*, J. Amer. chem. Soc. *74*, 278 (1952).

[9] *F. L. Scott, M. T. Kennedy*, and *J. Reilly*, J. Amer. chem. Soc. *75*, 1294 (1953).

II. The Chemistry of 1-Guanylpyrazoles

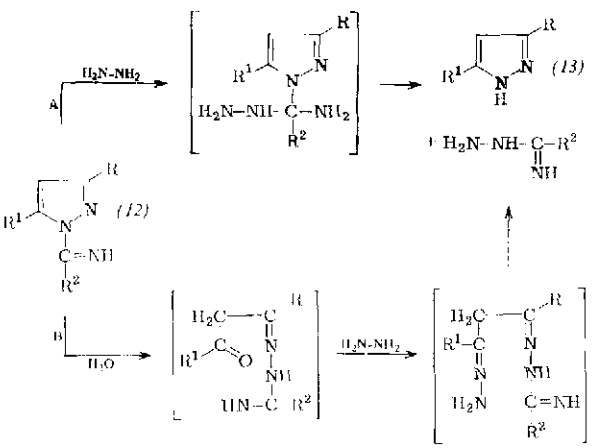
1-Guanylpyrazoles and 1-nitroguanylpyrazoles may be formally regarded as cyclic aminoguanidines, and are therefore briefly discussed.

3,5-Dimethyl-1-guanylpyrazole is sufficiently stable to withstand boiling acetic anhydride in acetic acid, or treatment for two hours with fuming nitric acid at 50 °C [11]. However, it is cleaved remarkably easily by hydrazines, amines, or azides.

1. *Hydrazinolysis*

The action of hydrazine hydrate on 3,5-dimethyl-1-guanylpyrazole *(12)* yields aminoguanidine and 3,5-dimethylpyrazole *(13)* [11, 12]. Use of an excess of hydrazine hydrate produces triaminoguanidine *(6)* [11, 12].

The reaction may proceed either by addition of the hydrazine molecule onto the 1-substituent and its subsequent detachment (A) or by initial hydrolytic ring-opening, followed by displacement of the ketonic oxygen by hydrazine and ring-closure (B). With hydrazine itself, the products from either



scheme would be identical, but an unsymmetrically substituted hydrazine such as phenylhydrazine would give rise to different products. Since 1-anilinoguanidine is in fact obtained together with 3,5-dimethylpyrazole, it appears that the reaction follows the first route (A).

3,5-Dimethyl-1-nitroguanylpyrazole is cleaved similarly by hydrazine [10] or phenylhydrazine [9] into 3,5-dimethylpyrazole and nitroaminoguanidine or 3-phenyl-1-nitroaminoguanidine, respectively. The reaction has been extended to many other hydrazines, including quinol-2-ylhydrazine, benzthiazol-2-ylhydrazine, and benzhydrazide [12].

[10] *F. L. Scott, M. T. Kennedy*, and *J. Reilly*, Nature (London) *169*, 72 (1952).

[11] *F. L. Scott, C. M. B. Murphy*, and *J. Reilly*, Nature (London) *167*, 1037 (1951).

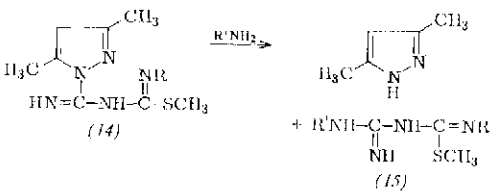
[12] *F. L. Scott, D. G. O'Donovan*, and *J. Reilly*, J. Amer. chem. Soc. *75*, 4053 (1953).

2. *Aminolysis*

The action of amines on 1-guanyl- or 1-nitroguanyl-3,5-dimethylpyrazole yields substituted guanidines together with 3,5-dimethylpyrazole [9, 10].

This reaction has been applied to heterocyclic bases, and to 1-guanylpyrazoles containing substituted guanyl groups. In many cases, the reaction proceeds as with the simple 1-guanyl compounds, but it is sometimes complicated by the formation of by-products. Thus, for example, on treating 1-benzoylguanyl-3,5-dimethylpyrazole with morpholine, a mixture of 1-(benzoylguanyl)morpholine and 1-[*N*-benzoyl-*N'*-(morpholino-1-yl)guanyl]morpholine is obtained [13].

The ease with which scission of the guanyl group occurs is strikingly illustrated by the observation that *S*-methylamidinothioureas *(15)* are obtainable on treatment of *S*-methylthioureides of type *(14)* with amines. At higher temperatures, however, further aminolysis yields trisubstituted biguanides [13].

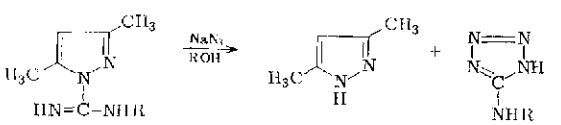


(14) *(15)*

Deguanylation of guanylpyrazoles is also brought about by other nucleophilic reagents such as sodium acetate [13]. Ethanolysis, although comparatively slow, is rapid enough for its progress to be followed spectrometrically [14].

3. *Azidolysis*

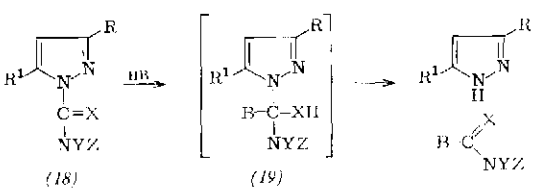
Deguanylation of 1-guanyl-3,5-dimethylpyrazole by boiling alcoholic sodium azide [13] gives 5-aminotetrazole *(16)* as the product other than 3,5-dimethylpyrazole. The corresponding 1-nitroguanyl derivative similarly affords 5-nitraminotetrazole *(17)* [13].



(16), R = H
(17), R = NO_2

4. *Mechanism of Deguanylation*

Preliminary studies suggested that deguanylation of guanylpyrazoles *(18)* proceeds by a mechanism involving slow formation of an adduct *(19)* followed by rapid elimination of part of the molecule [12]. The readiness with which the initial condensation occurs thus presumably depends upon the ease with which the substituted hydrazine or amine anion is attached to the carbonium ion; the more electrophilic the latter, the more readily should reaction take place [12].

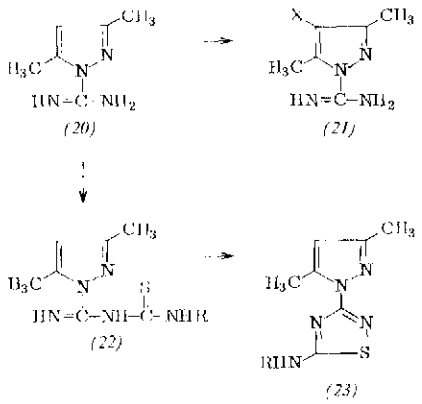


(18) *(19)*

From the results of a large number of pyrazole deacylations [10, 12, 13] it was indeed concluded that the mechanism was of the $B_{Ac}2$-type [14], analogous to that operating in many ester hydrolyses [15]. Support for this mechanism is provided by the effect of various substituents on the rate of ethanolysis of 1-guanylpyrazoles; it is probably the operative mode of deguanylation with amines and hydrazines [15]. In the deacylation of 3,5-dimethyl-1-(*N*,*N*-diphenyl-carbamyl)pyrazole *(19)*, R – R' = CH_3, X = O, Y = Z = C_6H_5, this $B_{Ac}2$ mechanism would appear to be the only possible one [16].

5. *Halogenation*

Chlorine and bromine rapidly halogenate 3,5-dimethyl-1-guanylpyrazole *(20)* to 4-chloro- or 4-bromo-3,5-dimethyl-1-guanylpyrazole *(21)* [11, 17]. Iodine reacts more slowly and, under the necessarily more drastic conditions required, deguanylation occurs with formation of 3,5-dimethyl-4-iodopyrazole.



(20) *(21)* *(22)* *(23)*

Condensation of 3,5-dimethyl 1-guanylpyrazole *(20)* (as the free base only) and aryl isocyanates or isothiocyanates gives the corresponding 1-thiocarbamyl derivatives *(22)* [17]. On reaction with halogens, these gave labile products that were difficult to isolate [17]. The final stable products proved to be oxidation products, which were correctly formulated [18] as pyrazolyl-1,2,4-thiadiazoles *(23)*, having previously been erroneously regarded as disulfides [17].

3,5-Dimethyl-1-nitroguanylpyrazole reacts analogously with bromine or chlorine to give 4-bromo or 4-chloro derivatives [9]. Under strongly alkaline conditions, partial deguanylation was responsible for the formation of some 4-halogeno-3,5-dimethylpyrazole [9]. Iodine and sodium acetate also gave a deguanylated product, but the 4-iodo derivative was obtained by treating the nitroguanylpyrazole with iodine monochloride in acetic acid [9].

III. Synthesis of Pyrazolones

Beyer and *Badicke* [19] showed that ethyl α-chloroacetoacetate is converted by amino- and nitroaminoguanidines into the correspondingly substituted hydrazone

[13] *F. L. Scott*, Chem. and Ind. *1956*, 547.

[14] *C. K. Ingold:* Structure and Mechanism in Organic Chemistry. Bell, London 1953, p. 752 *et seq.*

[15] *F. L. Scott*, Chimia *11*, 163 (1957).

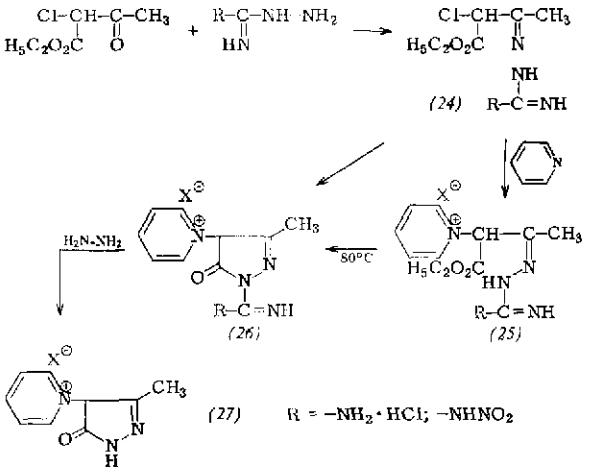
[16] *F. L. Scott*, *A. Ahearne*, and *J. Reilly*, J. org. Chemistry *22*, 1688 (1957).

[17] *F. L. Scott* and *J. Reilly*, J. Amer. chem. Soc. *74*, 4562 (1952).

[18] *F. L. Scott*, Chem. and Ind. *1958*, 463.

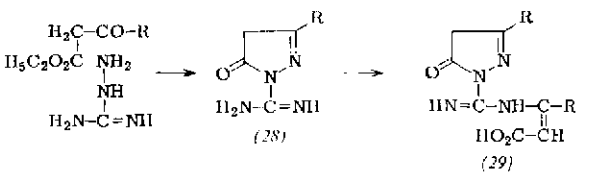
[19] *H. Beyer* and *G. Badicke*, Chem. Ber. *93*, 826 (1960).

hydrochlorides *(24)*. Further treatment of *(24)* with bases *(e.g.* pyridine, piperidine, or aniline) replaces the α-chlorine atom to yield ethyl α- pyridinioacetoacetate guanylhydrazone chloride *(25)*. Boiling ethanolic pyridine eliminates a molecule of alcohol either from the hydrazone *(24)* or from *(25)* to afford 1-guanyl-3-methyl-4-pyridiniopyrazol-5-one chloride *(26)*, an enol-betaine hydrochloride [19].



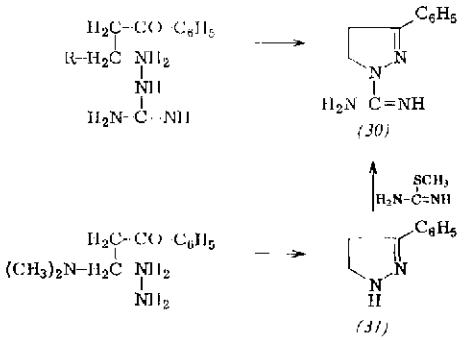
The formal resemblance of 1-guanylpyrazolones and 1-guanylpyrazoles (see above) is reflected in their analogous hydrazinolysis and aminolysis. Thus, treatment of 1-guanyl-3-methyl-4-pyridiniopyrazol-5-one chloride *(26)* with an excess of hydrazine hydrate yields 3-methyl-4-pyridinio-5-pyrazolone halide *(27)* and aminoguanidine. The production and hydrazinolysis of the corresponding 1-nitroguanyl compounds occurs in parallel fashion [19].

Like other hydrazine derivatives, aminoguanidine reacts with unsubstituted β-oxo-esters to form pyrazolones directly. *Vystrcil* and *Prokes* [20] prepared a number of these compounds and studied their infrared spectra [21]. 1-Guanyl-3-methyl-5-pyrazolone *(28)*, the simplest member of the series, first prepared by *De* [22], was obtained from aminoguanidine nitrate and ethyl acetoacetate. With an excess of the ester, the heterocyclic compound *(28)* continued to react to form *(29)*. Analogous compounds resulted from other esters such as benzoylacetic ester [20, 21].



IV. Synthesis of Pyrazolines

Condensation of aminoguanidine with a number of Mannich bases derived from acetophenone (or their oximes) [5, 23] yields 1-guanyl-3-phenyl-Δ²-pyrazoline *(30)*. Since the substituted amino moiety is lost from each Mannich base, the same pyrazoline *(30)* is obtained from different bases.



Since the possible formulation of the product as isomeric phenyl vinyl ketone guanylhydrazone had to be considered, and could not be excluded on the basis of ultraviolet and infrared spectra, an attempt was made to synthetize the pyrazoline *(30)* by an unambiguous route [23]: Authentic 3-phenyl-Δ²-pyrazoline *(31)* was converted with *S*-methylisothiouronium nitrate into a compound identical with the pyrazoline obtained from the Mannich bases. A possibility of ring-opening exists, but appears unlikely; however, reaction at the *N*(2)-nitrogen atom might also occur [23].

When treated with aminoguanidine, phenyl vinyl ketone also furnished a small yield of 1-guanyl-3-phenyl-Δ²-pyrazoline *(30)* [23].

B. 1,2,4-Triazoles

Aminoguanidine and its derivatives have been widely used in the synthesis of 3-amino-1,2,4-triazoles [2, 24]. Suitable intermediates are produced from aminoguanidine by acylation, or interaction with isothiocyanates, cyanates, or carbodiimides, or by direct synthesis by application of general methods.

I. Cyclization of Acylaminoguanidines

1. *Acylation of Aminoguanidine with Aliphatic Acids*

The classical synthesis of amino-1,2,4-triazoles introduced by *Thiele* [1, 25] involves acylation of aminoguanidine at the hydrazino moiety and cyclization of the resulting intermediate with alkali to the 3-amino-5-substituted-1,2,4-triazole.

The parent compound of the series, 3-amino-1,2,4-triazole, was first prepared by this method by *Thiele* and *Manchot* [26] using formic or oxalic acids, and has attracted much attention in recent years as a plant growth regulator [24, 27]; two satisfactory laboratory preparations based on *Thiele*'s synthesis have been

[20] *A. Vystrcil* and *R. Prokes*, Chem. Listy *46*, 670 (1952); Chem. Abstr. *48*, 165 (1954).

[21] *A. Vystrcil* and *R. Prokes*, Chem. Listy *47*, 160 (1953); Chem. Abstr. *48*, 3349 (1954).

[22] *S. C. De* and *P. C. Rakshit*, J. Indian chem. Soc. *13*, 509 (1936).

[23] *F. L. Scott* and *M.T. Scott*, Chimia *12*, 148 (1958).

[24] *K.T. Potts*, Chem. Reviews *61*, 87 (1961).

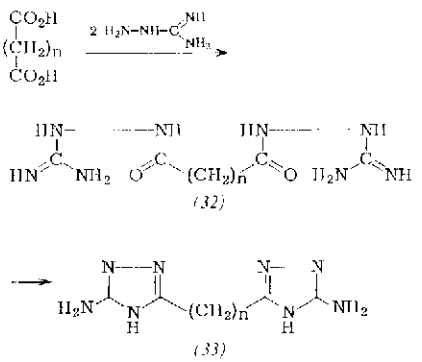
[25] *J. Thiele* and *K. Heidenreich*, Ber. dtsch. chem. Ges. *26*, 2598 (1893).

[26] *J. Thiele* and *W. Manchot*, Liebigs Ann. Chem. *303*, 33 (1898).

[27] *C. J. Grundmann* and *A. Kreutzberger*, U.S.-Pat. 2763661; Chem. Abstr. *51*, 3669 (1957).

described in detail [28, 29]. A recent patent [30] describing a preparation of this type suggests that the presence of an entraining agent to remove the water formed may be beneficial. Other triazoles prepared directly from aliphatic acids and aminoguanidine include 5-ethyl-, 5-propyl-, 5-isopropyl-, and 5-hexyl-3-amino-1,2,4-triazoles [31].

Dibasic aliphatic acids yield diguanidyl-dicarboxamides *(32)* in this condensation; they are advantageously isolated as mineral acid salts. Cyclization to the corresponding 'linked' triazole *(33)* is carried out in the normal manner by heating with aqueous potassium carbonate [32]. The diaminoditriazoles *(33)* can be diazotized and are said to give excellent dyes when coupled with ß-naphthol.

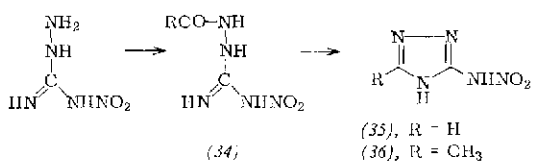


(32)

(33)

2. *Acylation of Nitroaminoguanidine*

Nitroaminoguanidine reacts with organic acids as does aminoguanidine; the intermediate acyl derivative *(34)* is cyclized to 3-substituted 5-nitroamino-1,2,4-triazoles by alkali. Thus, reaction with formic or acetic acid yields 3-nitramino- *(35)* or 3-methyl-5-nitramino-1,2,4-triazole *(36)*, respectively [33].



(34)

(35), R = H
(36), R = CH_3

The pyrazoline *(30)* resists bromination and aminolysis. This inactivity is striking contrast to the reactivity of the corresponding pyrazoles and pyrazolones, and may be ascribed to inability of the partly reduced ring to form a stable anion [23].

3,5-Dinitramino-1,2,4-triazole has been obtained by *Henry, Skolnik*, and *Smith* [34] by diazotizing 1,6-dinitro-2-aminoguanylbiguanidine: the unstable intermediate tetrazole decomposed to yield the nitraminotriazole among other products.

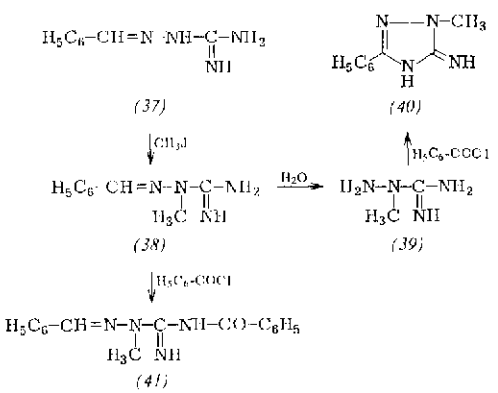
Nitraminotriazoles are fairly strong acids [35, 36] capable of forming salts [33, 34] and are convertible by reduction into the corresponding 3-hydrazino derivatives [34, 37]. 3-Hydrazino-1,2,4-triazole has been used for the preparation of a compound containing two triazole rings linked in the 1,3-positions [31]: thus 3,5-dimethyl-1-(1,2,4-triazol-3-yl)-1,2,4-triazole was obtained in 9 % yield by heating the hydrazino-triazole with diacetamide in acetic acid.

3. *Acylation of Aminoguanidine by Aromatic Acids and their Derivatives*

Unlike their aliphatic counterparts, aromatic acids react only reluctantly with aminoguanidine. Thus the action of benzoic acid afforded only very poor yields of 3-amino-5-phenyl-1,2,4-triazole [31], and salicylic acid failed to react [31]. On the other hand, good yields of triazoles were obtained from pyridine-2- or 3-carboxylic acids [31].

Considerable attention has therefore been given to aroylation of aminoguanidine with aromatic acid chlorides. *Benack* [38] claimed that 3-amino-5-phenyl-1,2,4-triazole was formed on heating aminoguanidine hicarbonate with benzoyl chloride. It appears more advantageous, however, to isolate the aroyl aminoguanidine, and to perform the cyclization separately [39]. Benzamidoguanidine is obtainable from benzoyl chloride and aminoguanidine in pyridine [39], or in benzene [40]; nicotinamido- and isonicotinamido-guanidine are also successfully prepared from the acid chlorides in pyridine [40, 41] and cyclized to triazoles by heating at 250 °C [40].

A disubstituted aminotriazole, *viz.* 5-amino-1-methyl-3-phenyl-1,2,4-triazole, is obtainable by this general method [31] as follows:



(37) *(40)* *(38)* *(39)* *(41)*

[28] *G. Sjostedt* and *L. Gringas*, Org. Syntheses, Coll. Vol. 3, Wiley, New York 1955, p. 95.

[29] *C. F. H. Allen* and *A. Bell*, Org. Syntheses *26*, 11 (1946).

[30] *M. Niese* and *D. Delfs*, U.S.-Pat. 2875209; Chem. Abstr. *53*, 17151 (1959).

[31] *M. R. Atkinson, A. Komzak, E. A. Parkes*, and *J. B. Polya*, J. chem. Soc. (London) *1954*, 4508.

[32] *N. R. Shreve* and *R. K. Charlesworth*, U.S.-Pat. 2744116; Chem. Abstr. *51*, 489 (1957).

[33] *R. A. Henry*, J. Amer. chem. Soc. *72*, 5343 (1950).

[34] *R. A. Henry, S. Skolnik*, and *G. B. L. Smith*, J. Amer. chem. Soc. *75*, 955 (1953).

[35] *J. E. DeVries* and *E. S. C. Gantz*, J. Amer. chem. Soc. *76*, 1008 (1954).

[36] *J. H. Boyer*, in *R. C. Elderfield:* Heterocyclic Compounds, Wiley, New York 1961, Vol. 7, p. 457.

[37] *E. Lieber, S. Schiff, R. A. Henry*, and *W. G. Finnegan*, J. org. Chemistry *18*, 218 (1953).

[38] *Benack*, Ph. D. Thesis, Universität München, 1896, p. 19; see Beilstein's Handbook, Vol. 26, 1st Suppl., p. 45.

[39] *E. Hoggarth*, J. chem. Soc. (London) *1950*, 612.

[40] *R. Giuliano* and *G. Leonardi*, Il Farmaco (Pavia), Ed. Sci. *9*, 529 (1954).

[41] *H. L. Yale, K. A. Losee, F. M. Perry*, and *J. Bernstein*, J. Amer. chem. Soc. *76*, 2208 (1954).

Benzylideneaminoguanidine *(37)* is methylated with methyl iodide, and the intermediate *(38)* hydrolysed to 1-amino-1-methylguanidine *(39)* which, on treatment with benzoyl chloride, yields the cyclized product *(40)* as a benzoyl derivative in one step. Direct reaction of benzoyl chloride with *(38)* does not result in cyclization, but only gives 1-benzylidineamino-3-benzoyl-1-methylguanidine *(41)*.

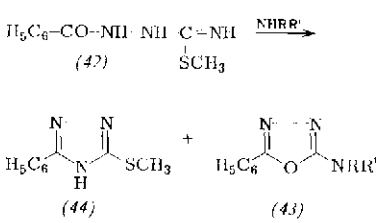
Since direct syntheses of acylamidoguanidines from aromatic acids or acid chlorides often give erratic results, indirect syntheses of the amides have been devised (see below).

4. *Reduction of Nitroguanidines in the Presence of Acids*

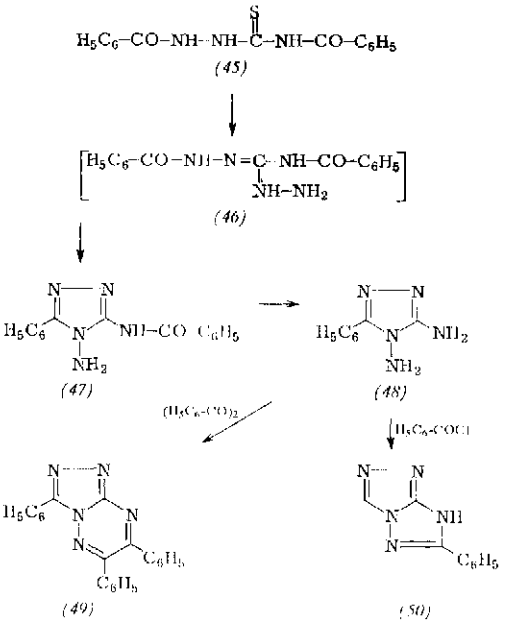
Reductions of nitroguanidine carried out in acetic acid produce 3-amino-5-methyl-1,2,4-triazole as a by-product [37, 42]. Nitroaminoguanidine similarly affords 3,4-diamino-5-methyl-1,2,4-triazole [37, 42] as a by-product, the structure of which is confirmed by diazotization in the presence of hypophosphorous acid, when removal of both amino groups yields the known compound 3-methyl-1,2,4-triazole [37] in 63 % yield. The initial diazotization product can be coupled with β-naphthol to afford the azo dye, 1-(3-methyl-1,2,4-triazol-5-yl)azo-2-naphthol, which is also obtainable by diazotization and coupling of 3-amino-5-methyl-1,2,4-triazole [37].

5. *Aminolysis of Acyl-S-alkylisothiosemicarbazides*

The action of ammonia or amines on 1-benzoyl-*S*-methylisothiosemicarbazide *(42)* does not yield the expected benzamidoguanidines [39] but affords a mixture of 2-amino-5-phenyl-1,3,4-oxadiazole *(43)* and 5-methylthio-3-phenyl-1,2,4- triazole *(44)* directly. The oxadiazoles probably arise from an intermediate aminoguanidine derivative by loss of a molecule of ammonia instead of water [39].

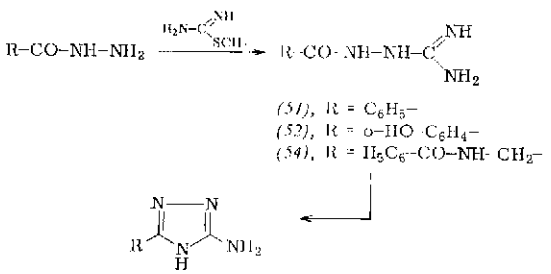


The interaction of 1,4-dibenzoylthiosemicarbazide *(45)* with hydrazine hydrate [43] proceeds with loss of hydrogen sulfide to yield a product formulated as 3,4-diamino-5-phenyl-1,2,4-triazole *(48)*, possibly arising via the hypothetical dibenzoyldiaminoguanidine *(46)*. Support for the structure *(48)* is provided by the formation of an *N,N'*-bis(benzylidene) derivative with benzaldehyde, and by its reaction with benzil to give a compound believed to be triphenyl-1,2,4,7,9-pentaazaindene *(49)* [43]. On treatment with benzoyl chloride, *(48)* gives a monobenzoyl derivative. Excess of the reagent yields a product with a composition which corresponds to a dibenzoyl derivative less one molecule of water. Mild hydrolysis produced a compound *(50)* believed to contain two fused rings [43].



6. *Synthesis of Acylaminoguanidines from Acylhydrazines*

The action of *S*-alkylisothiourea on acylhydrazines has proved a good general method for the synthesis of acylaminoguanidines and thence of 1,2,4-triazoles. Thus, 1-benzamidoguanidine *(51)* is easily obtained from benzhydrazide and *S*-methylisothiouronium sulfate in the presence of alkali [39]. 1-Salicylamidoguanidine *(52)* is prepared similarly and is readily cyclized to 3-amino-5-(*o*-hydroxyphenyl)-1,2,4-triazole *(53)* [31].



(51), R = C_6H_5–
(52), R = o-HO-C_6H_4–
(54), R = H_5C_6–CO–NH–CH_2–

(53), R = o-HO-C_6H_4–
(55), R = H_5C_6–CO–NH–CH_2

Biemann and *Bretschneider* [44] have described a number of further applications of this synthesis: Benzamidoacetyl hydrazide presumably affords the appropriate intermediate *(54)*, which cyclizes spontaneously with loss of water to 3-amino-5-benzamidomethyl-1,2,4-triazole *(55)*; final debenzoylation in acid medium slowly yields 5-aminomethyl-1,2,4-triazole. In a similar manner, both the 3-amino-5-(2-benzamidoethyl)- and 3-amino-5-(1-acetylamino-2-phenylethyl)-1,2,4-triazoles were prepared and were deacylated to the diamines [44].

1-Isonicotinamidoguanidine, prepared from isonicotinoylhydrazin, had a m.p. of 276 277 °C [44], but no reference was made to that previously reported (m.p. 177 °C) by *Giuliano* and *Leonardi* [40]. Pyrolysis at 200 °C cyclized 1-isonicotinamidoguanidine to 3-amino-5-(pyrid-3-yl)-1,2,4-triazole, which had the same m.p. (277 °C) as that previously reported (273–274 °C) [40]. The possibility of the supposed intermediate being a hydrate of the triazole was rejected on the grounds that the ultraviolet spectra of the two compounds were different.

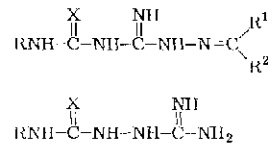
[42] *F. L. Scott, D. A. O'Sullivan,* and *J. Reilly,* J. appl. Chem. *2*, 184 (1952).

[43] *E. Hoggarth,* J. chem. Soc. *1950*, 614.

[44] *K. Biemann* and *H. Bretschneider,* Monatsh. Chem. *89*, 603 (1958).

II. Cyclization of Aminoguanyl(thio)ureas and Guanylthiosemicarbazides

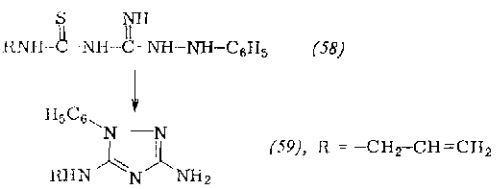
Interaction of aminoguanidine with isocyanates or isothiocyanates gives rise either to substituted *N*-(1-aminoguanyl)-ureas or -thioureas *(56)* or to 4-substituted 1-guanyl(thio)semicarbazides *(57)*, in the presence or absence, respectively, of a blocking group on the hydrazine residue. Both series of products are readily cyclized to 1,2,4-triazoles.



(56), X = O, S

(57), X = O, S

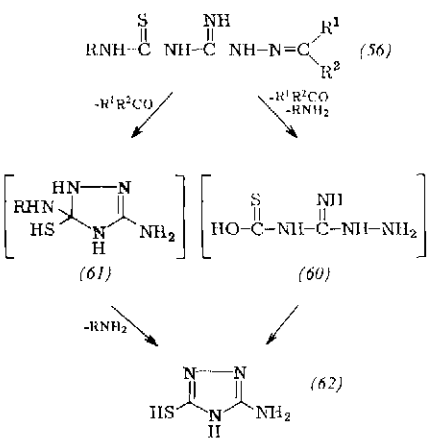
Addition of allyl or phenyl isothiocyanate onto 1-anilinoguanidine yields the expected *N*-(1-anilinoguanyl)thiourea derivative *(58)* [45]; the allyl homologue has been cyclized by alkali to give 5-allylamino-3-amino-1-phenyl-1,2,4-triazole *(59)* [45].



(58)

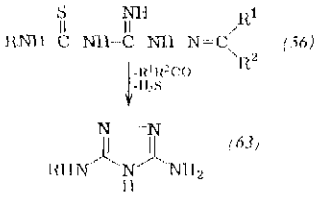
(59), R = $-CH_2-CH=CH_2$

1-Substituted 3-(1-aminoguanyl)thioureas, which have been obtained only in the form of hydrazones *(56)* [46], are cyclized by mineral acids to 3-amino-5-mercapto-1,2,4-triazole *(62)* in excellent yields. A mechanism for this general reaction involving the hypothetical 1-aminoguanylthiocarbamic acid *(60)* has been considered [46], but an addition-elimination mechanism involving an intermediate of type *(61)* may be more likely.



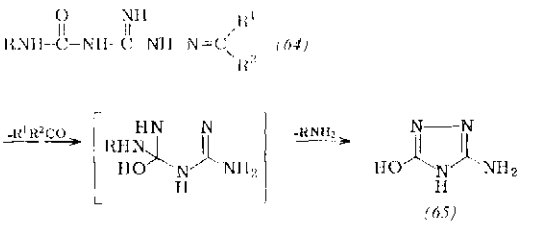
(56), *(61)*, *(60)*, *(62)*

The action of weak acids, or of alkalis, results in an alternative ring closure of *(56)*, involving loss of hydrogen sulfide to give 3,5-diamino-1,2,4-triazoles *(63)* [46].



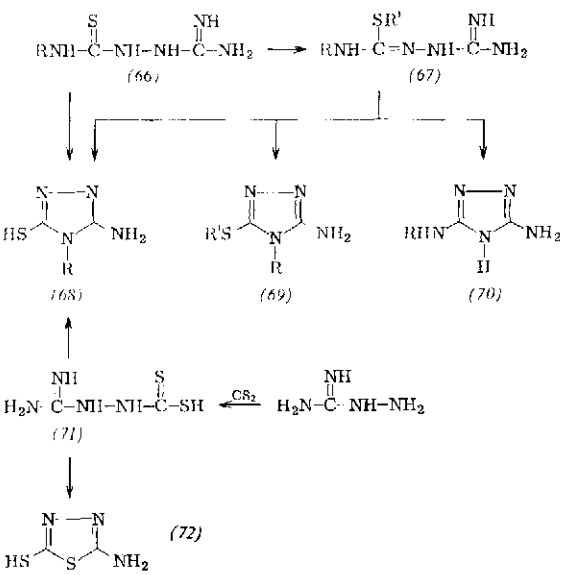
(56), *(63)*

The hydrazones in the corresponding urea series *(64)* are also cyclized by strong acids, albeit more slowly than the sulfur analogues, to form 3-amino-5-hydroxy-1,2,4-triazole *(65)* [46].



(64), *(65)*

The action of phenyl isothiocyanate on aminoguanidine hydrogen carbonate in ethanol was originally shown [45] to result directly, with loss of ammonia, in 3-amino-5-mercapto-4-phenyl-1,2,4-triazole *(68)*, R = C_6H_5. 4-Substituted 1-guanylthiosemicarbazides *(66)* are obviously concerned as intermediates in this reaction and were isolated as salts by *Fry* and *Lambie* [47], when



(66), *(67)*, *(68)*, *(69)*, *(70)*, *(71)*, *(72)*

aminoguanidine hydrochloride or nitrate were employed. They are rapidly converted into 4-substituted 3-amino-5-mercapto-1,2,4-triazoles *(68)* by alkalis [48] or, more slowly, in acid media, so that both products *(66)* and *(68)* are obtained side by side on prolonged interaction of aminoguanidine salts and isothiocyanates, particularly aromatic isothiocyanates [49]. Use of dimethylformamide as solvent and isolation of

[45] *P. Fantl* and *H. Silbermann*, Liebigs Ann. Chem. *467*, 274 (1928).

[46] *L. E. A. Godfrey* and *F. Kurzer*, J. chem. Soc. (London) *1960*, 3437.

[47] *D. J. Fry* and *A. J. Lambie*, Brit. Pat. 741280; Chem. Abstr. *50*, 16842 (1956).

[48] *D. J. Fry* and *A. J. Lambie*, Brit. Pat. 741228; Chem. Abstr. *50*, 9913 (1956).

[49] *L. E. A. Godfrey* and *F. Kurzer*, J. chem. Soc. (London) *1961*, 5137.

the products as crystalline toluene-*p*-sulfonates greatly facilitate production of the 4-substituted thiosemicarbazides *(66)* [49].

Benzylation of *(66)*, R = C_6H_5, yields the corresponding *S*-benzyl ether *(67)* which, like the parent compound *(66)*, also undergoes cyclization readily [49]. Boiling alkali removes the benzylthio residue as a whole and affords 3-amino-5-anilino-1,2,4-triazole *(70)* in excellent yield. Boiling aniline acts on *S*-benzyl-1-guanyl-4-phenylisothiosemicarbazide *(67)*, R = C_6H_5, R' = $C_6H_5CH_2$ in two distinct ways. The free base *(67)* yields approximately equal quantities of 3-amino-5-benzylthio-4-phenyl- *(69)* and 3-amino-5-anilino-1,2,4-triazole *(70)*; the toluene-*p*-sulfonate of *(67)*, on the other hand, gives 3-amino-4-phenyl-5-mercapto-1,2,4-triazole *(68)* almost quantitatively; in the latter case, the *S*-alkyl derivative is simply dealkylated, and the resulting parent compound *(66)* subsequently cyclizes in the usual way [49].

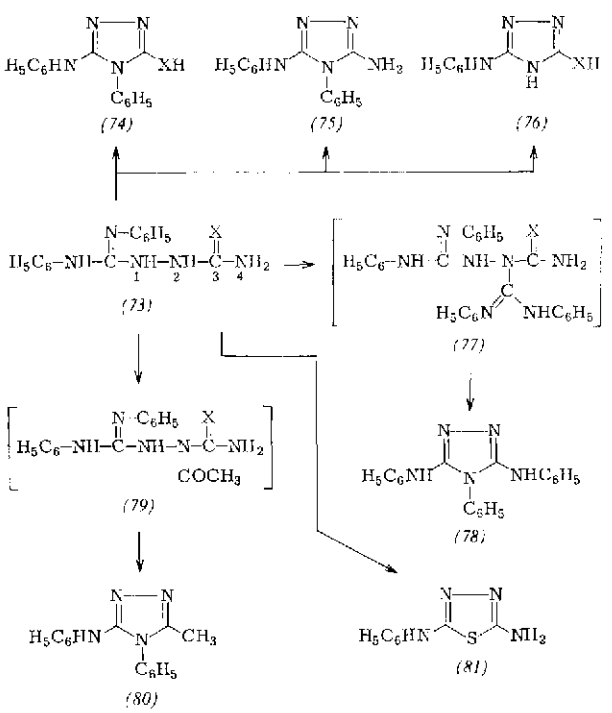
A closely related triazole synthesis involves production of guanidinodithiocarbamic acids *(71)* from aminoguanidine bicarbonate and carbon disulfide in acetic acid [51] and their cyclization in basic media [52]; a mixture of 3-amino-5-mercapto-1,2,4-triazole *(68)*, R = H and 2-amino-5-mercapto-1,3,4-thiadiazole *(72)* is obtained, the former predominating when higher temperatures and stronger alkalis are employed. Substituted aminoguanidines yield the appropriate homologues of *(68)* in this reaction.

Addition of diphenylcarbodiimide onto thiosemicarbazide yields 1-(*N*,*N*'-diphenylguanyl)thiosemicarbazide *(73)*, X = S [54], which may be formally regarded as an aminoguanidine derivative. In common with suitably substituted thiosemicarbazides in general [50], *(73)* undergoes cyclization readily, being converted into the appropriate 1,3,4-thiadiazole *(81)* in acidic, and into 1,2,4-triazoles, *(74)* and *(75)*, in alkaline media. Pyrolysis of *(73)*, results in loss of aniline and exclusive formation of 3-anilino-5-mercapto-1,2,4-triazole *(76)*, X = S [54].

1-(*N*,*N*'-Diphenylguanyl)semicarbazide *(73)*, X = O, is converted pyrolytically, or by alkaline hydrolysis, with loss of ammonia, into 3-anilino-5-hydroxy-4-phenyl-1,2,4-triazole *(74)*, X = O. Successive treatment of *(73)*, X = O, with acetic anhydride and alkali yields 3-anilino-5-methyl-4-phenyl-1,2,4-triazole *(80)*, presumably by the route *(73)* → *(79)* → *(80)* [54].

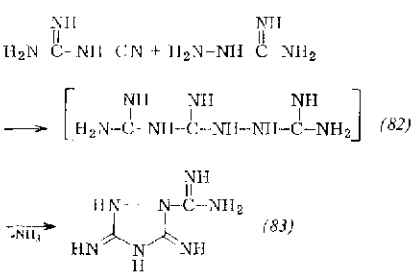
Further action of diphenylcarbodiimide on either 1-(*N*,*N*'-diphenylguanyl)thiosemicarbazide *(73)*, X = S, or 1-(*N*,*N*'-diphenylguanyl)-semicarbazide *(73)*, X = O, affords good yields of 3,5-dianilino-4-phenyl-1,2,4-triazole *(78)*, probably by way of the intermediate *(77)*, X = S or O [54].

Interaction of diphenylcarbodiimide and 4-phenylthiosemicarbazide does not result in simple addition: the monoadduct apparently cyclizes immediately with elimination of hydrogen sulfide or aniline to yield a mixture of 3,5-dianilino-4-phenyl-1,2,4-triazole *(78)* and (mainly) 3-anilino-5-mercapto-4-phenyl-1,2,4-triazole *(74)* X = S [54].



III. Synthesis of Triazoles from Biguanidines

Addition of dicyandiamide onto aminoguanidine yields 3,5-diimino-1-guanyl-1,2,4-triazolidine *(83)*, presumably by spontaneous cyclization, with loss of ammonia, of the intermediate 1-guanylbiguanidine *(82)* [53].



Interaction of excess aminoguanidine and diphenylcarbodiimide in dimethylformamide produces 1,2-diphenylbiguanidine *(84)* and 1-guanyl-4-phenyl-3,5-diphenylimino-1,2,4-triazolidine *(86)* in approximately equal proportions [54]. These compounds probably arise by successive addition of two moles of carbodiimide, one to each of the nitrogen atoms of the hydrazino group in aminoguanidine, followed by elimination of aniline [*(84)* → *(85)* → *(86)*]. The triazolidine *(86)* is in fact prepared more advantageously by the action of a second mole of carbodiimide on 1,2-diphenylbiguanidine *(84)*. The 4-imino-group in the biguanidine *(84)* thus acts as a particularly active centre, competing

[50] *W. R. Sherman*, in *R. C. Elderfield:* Heterocyclic Compounds. Wiley, New York 1961, Vol. 7, p. 587 *et seq.*

[51] *D. J. Fry* and *A. J. Lambie*, Brit. Pat. 737567; Chem. Abstr. *50*, 13086 (1956).

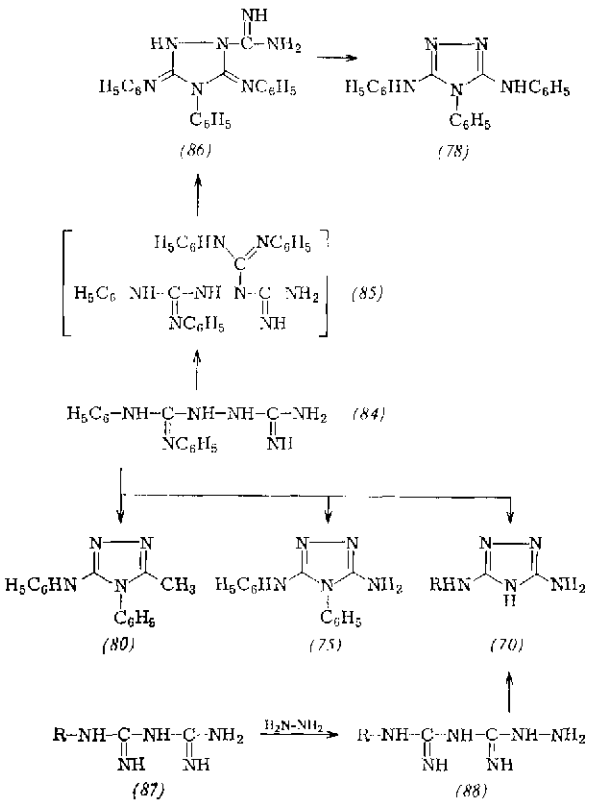
[52] *D. J. Fry* and *A. J. Lambie*, Brit. Pat. 737568; Chem. Abstr. *50*, 13097 (1956).

[53] *J. K. Simons*, U.S.-Pat. 2456090; Chem. Abstr. *43*, 3843 (1949).

[54] *L. E. A. Godfrey* and *F. Kurzer*, J. chem. Soc. (London) *1962*, 3561.

strongly for the available carbodiimide, since *(84)* and *(86)* are formed side by side, even when an excess of aminoguanidine is employed [54].

1-Guanyl-4-phenyl-3,5-diphenylimino-1,2,4-triazolidine *(86)* is converted rapidly and almost quantitatively into 3,5-dianilino-4-phenyl-1,2,4-triazole *(78)* by hydrolysis. As expected, this triazole is also the direct product of the interaction of aminoguanidine and diphenylcarbodiimide in the molar proportion 1:2 [54].



1,2-Diphenylbiguanidine *(84)* is a diacidic base, which is stable towards acids and alkalis, but is pyrolysed at 160 °C, with loss of either ammonia or aniline, to give 3-amino-5-anilino-4-phenyl-1,2,4-triazole *(75)* and 3-amino-5-anilino-1,2,4-triazole *(70)* side by side. Acetylation of *(84)* and subsequent treatment with alkali yields 3-anilino-5-methyl-4-phenyl-1,2,4-triazole *(80)* probably by way of the intermediate acetyl derivative *(79)*, X = NH, followed by the well established dehydrative cyclization (see Sections B I, 1–3) with simultaneous removal of the guanyl side-chain at *N*-1 [54].

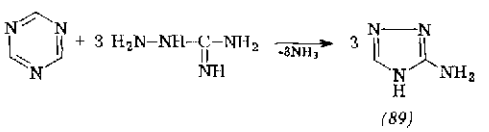
IV. Synthesis of Triazoles from Biguanides

Substituted amino- or diaminoguanidines are likely intermediates in the synthesis of certain 3-amino- or 3-hydrazino-1,2,4-triazoles from biguanides. Thus, the formation of 3-amino-5-(*p*-hydroxyanilino)-1,2,4-triazole *(70)*, by the action of hydrazine on *p*-hydroxyphenylbiguanide *(87)* probably proceeds via the guanylaminoguanidine *(88)* (R = *p*-HO-H_4C_6 in each case) [55]. Other reactions of this type entail additions of hydrazine or acylated hydrazines onto dicyandiamide to produce 3,5-diamino-1,2,4-triazole [56], or 1-acyl-3,5-diamino-1,2,4-triazoles [53], respectively. Semicarbazide, thiosemicarbazide, and hydrazides react analogously.

Another group of reactions that may possibly involve transitory formation of aminoguanidines is the hydrazinolysis of esters of *N,N*-dimethyldithiocarbamic acids to give thiols and 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole [57].

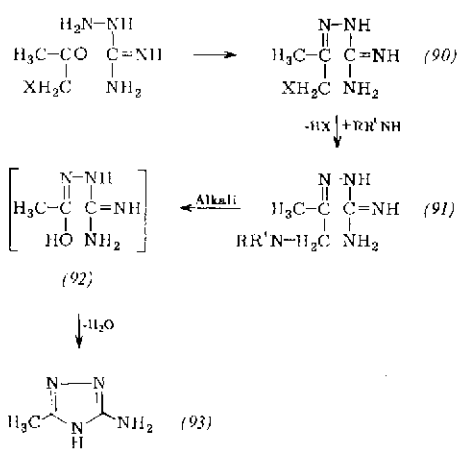
V. Synthesis of Triazoles from s-Triazine

An interesting conversion of *s*-triazine into the more stable triazoles was discovered by *Grundmann* and *Kreutzberger* [27, 58], who found that *s*-triazine reacts readily with semicarbazide, thiosemicarbazide, or aminoguanidine to give 3-substituted 1,2,4-triazoles. Thus, the action of freshly liberated aminoguanidine base on *s*-triazine gave a 47 % yield of 3-amino-1,2,4-triazole *(89)*.



VI. Other Syntheses of Triazoles

A novel synthesis of 3-amino-5-methyl-1,2,4-triazole *(93)*, reported by *Beyer* and *Pyl* [59], makes use of guanyl- and nitroguanylhydrazones of ω-halogeno-ketones *(90)*. These react with many organic nitrogen bases to form derivatives *(91)* that are stable and may be isolated as salts. The salts are cleaved by alkali into methanol, the appropriate base, and acylaminoguanidine *(92)*, which then cyclizes with loss of water to the triazole *(93)*.



C. Thiadiazoles

The condensation of aminoguanidine with certain compounds containing sulfur gives rise to structures that are suitable intermediates for the production of 1,3,4-thiadiazoles.

[55] *G.F. D'Alelio*, U.S.-Pat. 2406591; Chem. Abstr. *41*, 488 (1947).

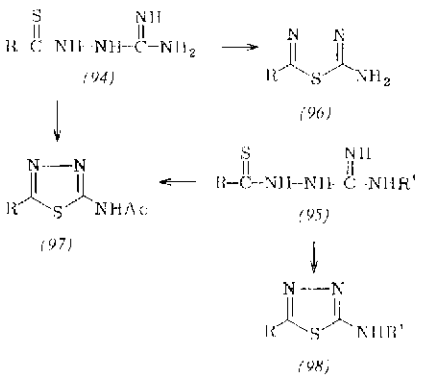
[56] *D.W. Kaiser, G. A. Peters*, and *V. P. Wystrach*, J. org. Chemistry *18*, 1610 (1953).

[57] *M. Kulka*, Canad. J. Chem. *34*, 1093 (1956).

[58] *C. J. Grundmann* and *A. Kreutzberger*, J. Amer. chem. Soc. *79*, 2839 (1957).

[59] *H. Beyer* and *T. Pyl*, Chem. Ber. *89*, 2556 (1956).

Thiobenzoylation with thiobenzoylthioacetic acid [62] of aminoguanidine [60, 61] or 1-amino-3-arylguanidines [61] yields *N*-(thiobenzamido)guanidine *(94)* or its 3-aryl analogues *(95)* which are readily cyclized to 1,3,4-thiadiazoles in acid media (compare the dehydrative cyclization of corresponding acylaminoguanidines to 1,2,4-triazoles in alkalis; cf. Sections B. I. 1–3). Phosphoric acid or acetic anhydride convert the parent compound *(94)*, with loss of ammonia, into 2-amino-5-phenyl-1,3,4-thiadiazole *(96)* or its acetyl derivative *(97)*, respectively [61]. Aryl analogues *(95)* afford the expected 2-arylamino-5-phenyl-1,3,4-thiadiazoles *(98)* on treatment with mineral acid, but lose arylamine to form 2-acetamido-5-phenyl-1,3,4-thiadiazole *(97)* under the influence of acetic anhydride [61].



4-Substituted 1-guanylthiosemicarbazides *(94)*, R = ArNH, obtained from aryl isothiocyanates and aminoguanidine, are cyclized similarly by phosphoric acid at 120–130 °C to give 2-amino-5-arylamino-1,3,4-thiadiazoles *(96)*, R = ArNH, in satisfactory yields [49]. Boiling acetic anhydride affords the corresponding diacetyl derivatives [49].

The cyclization of the structurally related compound guanidinodithiocarbamic acid *(71)* [51, 52] has already been discussed (cf. Section B. II).

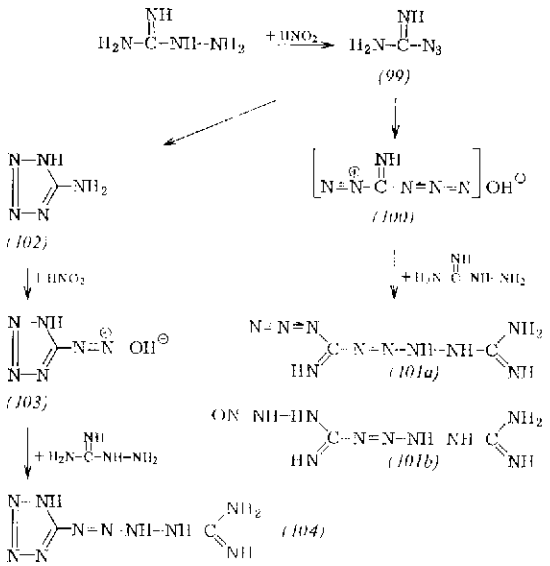
D. Tetrazoles

I. Reaction between Nitrous Acid and Aminoguanidine

Thiele [1] was the first to investigate the action of nitrous acid on aminoguanidine, and his interesting observations have prompted many other studies of these reactions. Their variable course and the instability of some of the products make this work difficult, and certain questions remain controversial. *Lieber* and *Smith* [2] have dealt with these reactions at length, and other briefer discussions have appeared in recent years [63–65]. The course of the reaction depends greatly on the acidity of the solution.

1. *Reaction in Neutral or Weakly Acidic Solution*

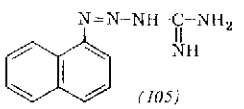
Hofmann and *Roth* [66] showed that neutral cold aqueous aminoguanidine nitrate reacts slowly with excess sodium nitrite over a period of days to produce an open-chain compound formulated as *(101a)* or *(101b)*, presumably by a sequence such as that shown. *Hofmann* and co-workers [67, 68] favoured the β-nitrosohydrazino structure *(101b)*; although *Lieber* and *Smith* [2] regard the evidence as conclusive, there still appears to be some room for speculation.



A different product *(104)* is obtained if guanyl azide *(99)*, formed as primary intermediate, cyclizes to 5-aminotetrazole *(102)*. This amine then reacts with a further molecule of nitrous acid to form a diazo-compound *(103)*, which couples with unreacted aminoguanidine to give guanyltetrazyltetrazene *(104)*. The two compounds *(101)* and *(104)* have been re-examined by *Hofsommer* and *Pestemer* [64], who attempted to confirm the assigned structures by an examination of the ultraviolet spectra of intermediate stages of known structure, but the results obtained were not entirely conclusive.

2. *Dyes from Diazotized Aminoguanidine*

Hofmann, *Hock*, and *Roth* [67] found that neutral solutions containing 'diazotized' aminoguanidine couple slowly with suitable intermediates, such as β-naphthol, to form colored compounds. *Shreve*, *Carter*, and *Willis* [65] reinvestigated this reaction, performing the cou-



pling at 80–85 °C. They proposed structure *(105)* for the product obtained from β-naphthol and claimed this to be the first example of a dye derived from an aliphatic diazo compound. Reduction gave 1-amino-2-naphthol, but aminoguanidine or its decomposition products could not be isolated.

[60] *K. A. Jensen* and *J. F. Miquel*, Acta chem. scand. *6*, 189 (1952).

[61] *F. Kurzer*, J. chem. Soc. (London) *1961*, 1617.

[62] *F. Kurzer*, Chem. and Ind. *1961*, 1333.

[63] *J. Reilly*, *J. P. Teegan*, and *M. F. Carey*, Sci. Proc. Roy. Dublin Soc. *24*, 349 (1948).

[64] *R. Hofsommer* and *M. Pestemer*, Z. Elektrochem. *53*, 383 (1949).

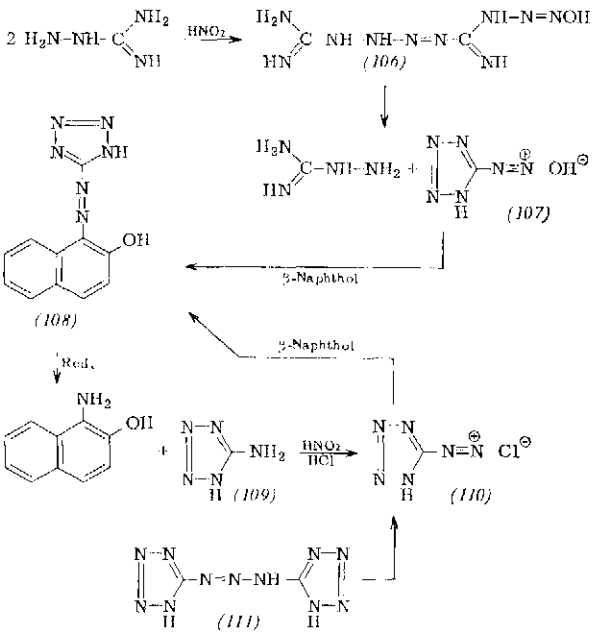
[65] *R. N. Shreve*, *R. P. Carter*, and *J. M. Willis*, Ind. Engng. Chem. *36*, 426 (1944).

[66] *K. A. Hofmann* and *R. Roth*, Ber. dtsch. chem. Ges. *43*, 682 (1910).

[67] *K. A. Hofmann*, *H. Hock*, and *R. Roth*, Ber. dtsch. chem. Ges. *43*, 1087 (1910).

[68] *K. A. Hofmann*, *H. Hock*, and *H. Kirmreuther*, Liebigs Ann. Chem. *380*, 131 (1911).

The reason for this became apparent when *Reilly* et al. [63] showed that the dye formed during the coupling process was actually a derivative of 5-diazotetrazole of structure *(108)*. The guanylnitrosoaminoguanyltetrazene



(106) initially formed splits into two fragments, one of which cyclizes to the tetrazole *(107)* and couples with the β-naphthol. 5-Aminotetrazole *(109)* can in fact be isolated as one of the reduction products of the dye *(108)* [63].

The structure of the dye *(108)* was confirmed by synthesis from diazotized 5-aminotetrazole *(110)* and suitable naphthols. The same dye also resulted from 1,3-ditetrazolyltriazene *(111)* and β-naphthol [67], at 80 °C, *(111)* being first split at the –NH–N=N link to form 5-aminotetrazole and tetrazolyldiazonium chloride.

3. *Reaction in Strongly Acid Solution: Guanyl Azide*

Thiele [1] was again the first to treat aminoguanidine with nitrous acid in strongly acid solution; the product was later [69] identified as guanyl azide nitrate. The corresponding sulfate has recently been prepared [64]. Nitroguanyl azide, obtained analogously from nitroaminoguanidine and nitrous acid [70–72], undergoes the same types of reaction as guanyl azide.

4. *Reactions of Guanyl Azides*

a) Conversion of Guanyl Azide into Guanidine or Aminoguanidine Derivatives

Treatment of guanyl azide with hydrazine hydrate displaces the azide radicle to give a good yield of aminoguanidine [73], together with small quantities of 5-aminotetrazole, which is formed as by-product by cyclization. The use of excess hydrazine hydrate produces mixtures of di- and triaminoguanidines, and this reaction has been suggested as a preparative method for these compounds [73]. Nitroguanyl azide similarly yields nitroaminoguanidine [72].

Guanyl azide nitrate and nitroguanyl azide are converted by aniline into phenylguanidine (70 %) [74] and 1-phenyl-3-nitroguanidine (75 %) [74], respectively. By a comparable azide displacement, phenylhydrazine yields 1-anilino-3-nitroguanidine from nitroguanyl azide [74].

Azide displacement appears to be the preferential mode of reaction when the basicity of the base is low, and its nucleophilic activity towards carbonyl carbon [74] is high. Aniline and phenylhydrazine fulfil both these conditions, but hydrazine hydrate causes a certain amount of tetrazole formation because of its higher basicity.

Reduction of nitroguanyl azide with hydrogen sulfide gives nitroguanidine in 90 % yield [71]. When attempts were made [72] to obtain the monoazide of diaminoguanidine by gently reducing nitroguanyl azide with sodium bisulfite, nitroguanidine was the actual product (58 %).

b) Cyclization of Guanyl Azide to Tetrazoles

The most valuable reaction of guanyl azide in heterocyclic synthesis is its ready cyclization by weak bases to 5-aminotetrazole [1]. The product is slightly acidic and can be separated either as a free acid or as the salt of an organic or inorganic base. Nitrous acid reacts with substituted aminoguanidines in acid conditions to give substituted guanyl azides, which are readily cyclized by weak bases to mono- or di-substituted tetrazoles [70, 71, 74–76]. Substituted guanyl azides, unlike their parent compound, may cyclize in two ways: With most alkyl- or aryl-guanyl azides, reaction proceeds almost exclusively by route (A), and yields of up to 95 % 1-alkyl- or 1-aryl-5-aminotetrazoles *(113)* [75] are obtained. A certain amount of 5-alkyl- or 5-arylaminotetrazole *(114)* is usually formed as a by-product [75]. The presence of an electronegative substituent (*e.g.* a nitro-group) promotes cyclization by the second route (B), and 5-nitraminotetrazole *(114)*, R = NO_2, becomes the main product [70, 71, 74].

The relative proportions of 5-alkylaminotetrazole *(114)* and 1-alkyl-5-aminotetrazole *(113)* resulting from cyclization of guanyl azides vary according to the conditions, because isomerization may take place simultaneously [75, 77]. This occurs readily at 180–200 °C and reaches an equilibrium in homogeneous systems (*e.g.* in solution in glycerol), the position of the equilibrium depending mainly on the electronegativity of the substituent [77]. Equilibrium is not necessarily attained above the melting point of the tetrazole: if the isomerized product melts at a higher temperature, the equi-

[69] *A. Hantzsch* and *A. Vogt*, Liebigs Ann. Chem. *314*, 339 (1900).

[70] *T. E. O'Connor, G. Fleming*, and *J. Reilly*, J. Soc. chem. Indust. *68*, 309 (1949).

[71] *E. Lieber, E. Sherman, R. A. Henry*, and *J. Cohen*, J. Amer. chem. Soc. *73*, 2327 (1951).

[72] *F. L. Scott, D. G. O'Donovan*, and *J. Reilly*, J. appl. Chem. *2*, 368 (1952).

[73] *T. E. O'Connor, K. Horgan*, and *J. Reilly*, J. appl. Chem. *1*, 91 (1951).

[74] *F. L. Scott, F. C. Britten*, and *J. Reilly*, J. org. Chemistry *21*, 1519 (1956).

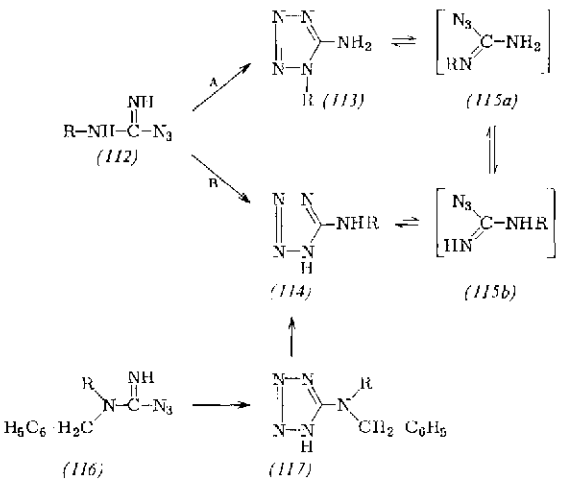
[75] *W. G. Finnegan, R. A. Henry*, and *E. Lieber*, J. org. Chemistry *18*, 779 (1953).

[76] *L. H. Schwartzman* and *B. B. Corson*, J. Amer. chem. Soc. *76*, 781 (1954).

[77] *R. A. Henry, W. G. Finnegan*, and *E. Lieber*, J. Amer. chem. Soc. *76*, 88 (1954).

librium is continually displaced by solidification. The isomerization probably involves initial ring-opening to form the substituted guanyl azide *(115)*, which exists in two isomeric forms, followed by recyclization in two ways [77] as shown. The relative proportion of the isomers *(113)* and *(114)* in a mixture can be determined by titrating the acidic 5-alkyl- or 5-arylaminotetrazoles *(114)* [77].

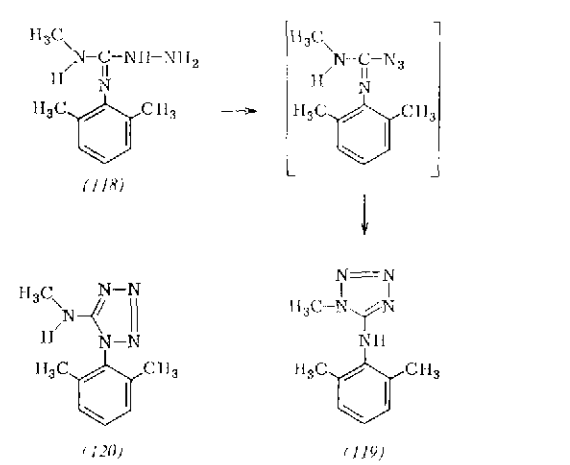
Although only small amounts of 5-aryl- or 5-alkylaminotetrazoles *(114)* are normally formed, they are easily isolated by precipitation as copper salts [75]. Decomposition with hydrogen sulfide yields the free amines [75], many of which are as strongly acidic as acetic acid [77].



Unequivocal proof of the structure of *(114)* is provided by synthesis from 1-alkyl-1-benzylaminoguanidine [75]. Ring closure of 1-alkyl-1-benzylguanyl azide *(116)* can occur in only one direction yielding 5-alkyl-5-benzyl-aminotetrazole *(117)*. Removal of the blocking benzyl group by catalytic hydrogenation [75] gives the desired tetrazole *(114)*.

Percival and *Herbst* [78] prepared a series of 1-alkyl-5-alkylaminotetrazoles with identical substituents by the general method. 1-Amino-2,3-dialkylguanidine was treated with nitrous acid and the resultant azide cyclized to the tetrazoles. This method failed, however, with 1-amino-2-benzyl-3-di-(β-cyanoethyl)guanidine[79].

The ready isomerization of substituted 5-aminotetrazoles and the two alternative modes of ring closure sometimes complicate the formulation of products. Thus, after carrying out a Schmidt reaction on 2,6-dimethylacetophenone, *Schwartzmann* and *Corson* [76] obtained a tetrazole which they formulated as 1-methyl-5-(2,6-dimethylanilino)tetrazole *(119)*, and then attempted to synthetize it by the supposedly unequivocal route *(118)* → *(119)*.

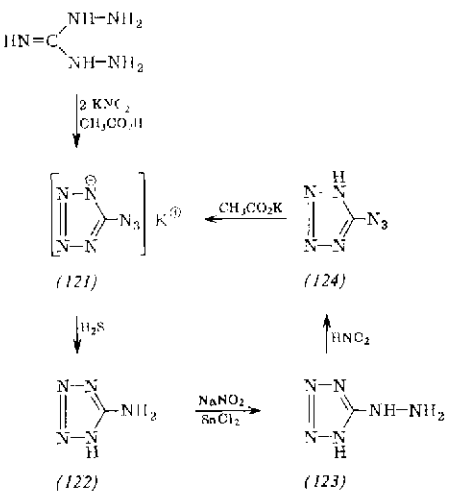


However, *Finnegan*, *Henry*, and *Olsen* [80] pointed out that comparable reactions usually yielded the isomeric 1-aryl-5-alkylaminotetrazoles [75]. Owing to steric hindrance, it was difficult to fix the structure by chemical means but infrared spectra indicated that *Schwartzmann* and *Corson*'s compound was in fact 5-methylamino-1-(2,6-dimethylphenyl)tetrazole *(120)* [80].

c) Cyclization of Guanyl Azide Derivatives Containing Electronegative Substituents

α) Reaction of 1,3-Diaminoguanidine with Nitrous Acid

In the reaction between 1,3-diaminoguanidine and nitrous acid in buffered or weakly acid solution, initial diazotization is followed by a more rapid cyclization than that which occurs with aminoguanidine [81]. The use of two moles of alkali nitrite yields the alkali salt of tetrazolyl azide *(121)* as the sole product [81].



Potassium tetrazolyl azide crystallizes as lustrous white platelets which are highly sensitive to pressure, friction, or heat; less than 0.01 g sometimes give rise to violent explosions, particularly if the product is contaminated with acetic acid. The free azide *(124)* prepared from 5-hydrazinotetrazole *(123)* is less sensitive to shock than the salts. The properties of this azide do not correspond with those reported by *Thiele* [1], but the structure he assigned to it was confirmed by infrared spectra and by reduction with hydrogen sulfide to the known compound 5-aminotetrazole *(122)*.

The use of only one equivalent of nitrous acid gave merely a diminished yield of *(121)* together with unchanged diaminoguanidine [81].

β) Nitroguanyl Azide

In its reaction with nitrous acid, 3-nitro-1-aminoguanidine behaves like 1,3-diaminoguanidine [70, 71]. In mineral acid solution, nitroguanyl azide *(125)* is produced [70, 71] as colorless platelets, m.p. 56 °C. In

[78] *D. F. Percival* and *R. M. Herbst*, J. org. Chemistry *22*, 925 (1957).

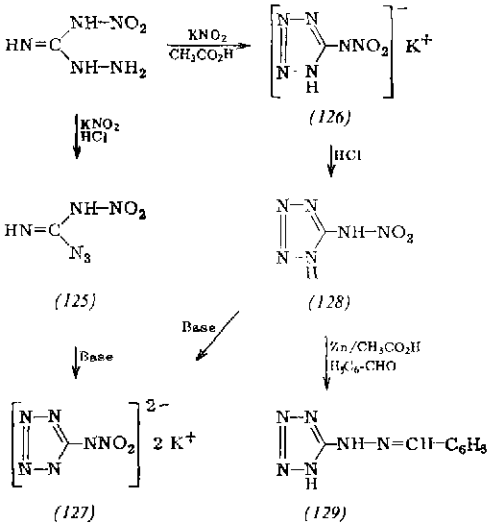
[79] *D. W. Renn* and *R. M. Herbst*, J. org. Chemistry *24*, 473 (1959).

[80] *W. G. Finnegan*, *R. A. Henry*, and *A. L. Olsen*, J. Amer. chem. Soc. *77*, 4420 (1955).

[81] *E. Lieber* and *D. R. Levering*, J. Amer. chem. Soc. *73*, 1313 (1951).

neutral or acetic acid solution, the alkali salt of 5-nitroaminotetrazole *(126)* is formed with alkali nitrite.

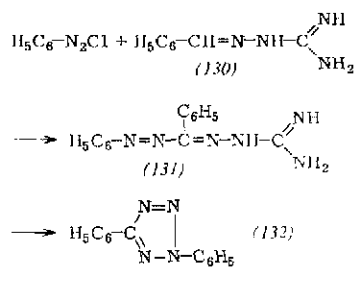
Nitroguanyl azide is cyclized almost quantitatively by dilute alkalis, including ammonium hydroxide [70–72] and organic bases [82], to di-salts of 5-nitroaminotetrazole *(127)*. Free 5-nitroaminotetrazole *(128)* is liberated from its salts by acids and is very sensitive to both mechanical and thermal shock and may explode violently [70, 71].

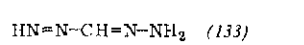


The structure of 5-nitroaminotetrazole was confirmed by reducing it with zinc and acetic acid to 5-hydrazinotetrazole, which was isolated as its benzylidene derivative *(129)*. The ultraviolet spectra of 5-nitroaminotetrazole and some of its salts have been described and a zwitterion structure has been proposed [83].

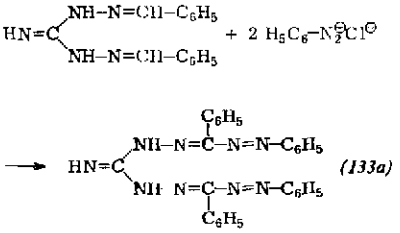
II. Synthesis of Tetrazoles from Aminoguanidine via Formazans

Towards the end of the nineteenth century, *Wedekind* [84] prepared so-called "guanazyl" compounds*(131)* by condensing aryldiazonium salts with the tertiary hydrogen in aldehyde guanylhydrazones *(130)*, usually in alkaline medium. These compounds were readily oxidized to 2,5-diaryltetrazoles *(132)*. The chemistry of formazans *(133)* has recently been reviewed by *Nineham* [85].





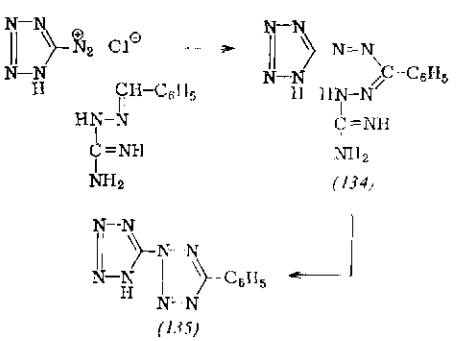
The coupling reaction has been extended to hydrazones derived from diaminoguanidine [86, 87]. Both their tertiary hydrogen atoms react with aryldiazonium salts in the expected manner to yield bis-(3,5-diarylformazan-1-yl)formimine *(133a)* [86, 87].



Ring-substituted aryldiazonium compounds were also applicable, but with regard to heterocyclic diazonium salts, only that derived from 4-aminoantipyrine underwent condensation.

Mild oxidation of the bisformazanylformimines *(133a)* did not yield the expected bis-(5-aryl-2-tetrazolyl)formimines, because oxidation was accompanied by fission, and only single-ring disubstituted tetrazoles, *e.g.* *(132)*, were obtained [86–88]. Concentrated nitric acid oxidizes and nitrates *(133a)* simultaneously yielding 2,5-di(nitrophenyl)-tetrazole as the main product [88].

An interesting attempt was made to prepare a system containing two tetrazole rings by oxidation of the formazan *(134)* obtained from tetrazole-5-diazonium chloride and 1-benzylideneaminoguanidine [89]. Concentrated nitric acid was unsuitable because it caused complete destruction, bromine gave tetrazines, but aqueous permanganate gave the desired product *(135)* in 70 % yield [89].



A logical extension of this work was the attempt to prepare formazans from derivatives of triaminoguanidine [87], the tris-benzylidene derivative *(136)* of which was coupled with a number of diazonium salts. The diazotates of *p*-nitroaniline, β-naphthylamine, and 4-chloro-2-toluidine coupled in the expected manner to form iminourea derivatives, *e.g.* *(137)*, but phenyldiazonium chloride behaved anomalously, introducing

[82] *E. Lieber, C. C. Herrick,* and *E. Sherman,* J. Amer. chem. Soc. *74,* 2684 (1952).

[83] *E. Lieber, E. Sherman* and *S. H. Patinkin,* J. Amer. chem. Soc. *73,* 2329 (1951).

[84] *E. Wedekind,* Ber. dtsch. chem. Ges. *30,* 444 (1897).

[85] *A. W. Nineham,* Chem. Reviews *55,* 355 (1955).

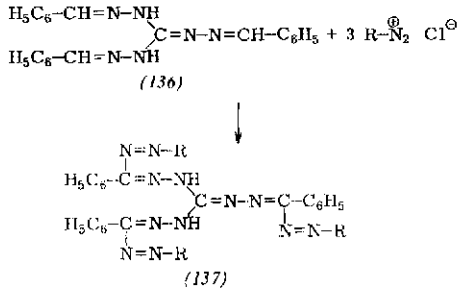
[86] *F. L. Scott, D. A. O'Sullivan,* and *J. Reilly,* J. chem. Soc. (London) *1951,* 3508.

[87] *F. L. Scott, D. A. O'Sullivan,* and *J. Reilly,* Chem. and Ind. *1952,* 782.

[88] *F. L. Scott, D. A. O'Sullivan,* and *J. Reilly,* J. Amer. chem. Soc. *75,* 5309 (1953).

[89] *V. A. Grakauskas, A. J. Tomasewski,* and *J. P. Horwitz,* J. Amer. chem. Soc. *80,* 3155 (1958).

only a phenoxy group [87]. All heterocyclic diazonium salts, excepting tetrazole-5-diazonium salts [87], failed to react.



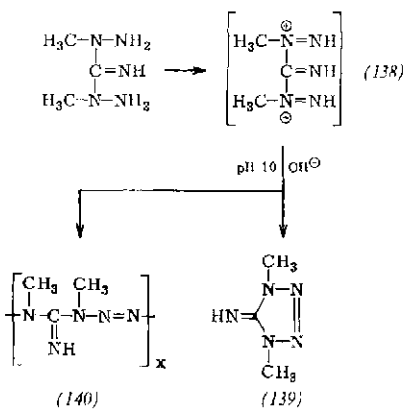
(136)

(137)

In the above coupling reactions, the diazonium compound may attack the aminoguanidine derivative at three centres, *viz.* the =CH-group, the –NH-group, or even in the aromatic ring. A number of problems are posed by this reaction [85], and *Scott* [88] has suggested that formazan formation is more likely when the carbon atom of the =CH-group is the centre of highest electron density. *Busch* et al. [90] postulated initial coupling of the diazonium ion at the nitrogen atom, followed by rearrangement of the tetrazene to a formazan.

III. Other Syntheses of Tetrazoles

A novel synthesis of tetrazoles from aminoguanidine derivatives has been developed by *McBride*, *Finnegan*, and *Henry* [91]. 1,2-Dimethyl-1,2-diaminoguanidine, prepared from 2,3-dimethylisothiosemicarbazide and methylhydrazine, was oxidized to a diazonium-like intermediate *(138)* with potassium bromate or iodate in 6 N hydrochloric acid. Subsequent basification (to pH 10) either cyclized the intermediate to 1,4-dimethyl-5-iminotetrazole *(139)* or converted it by intermolecular coupling into a water-soluble polytetrazene *(140)*.



(138)

(140) *(139)*

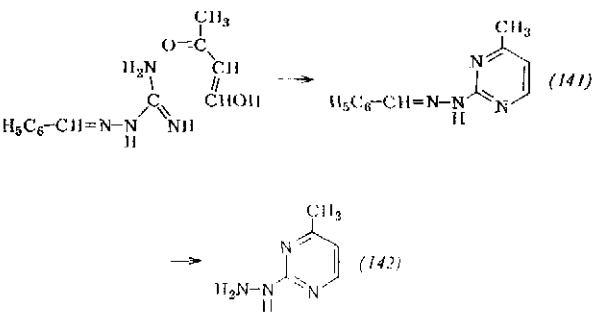
The tetrazole *(139)* was isolated by further reaction with phenyl isothiocyanate and separation of the resultant 1-(1,4-dimethyltetrazolyl)-3-phenylthiourea [91]. The polytetrazene *(140)* could not be isolated, and its formation was only adduced from spectroscopic evidence.

[90] *M. Busch* and *H. Pfeiffer*, Ber. dtsch. chem. Ges. *59*, 1162 (1926); *M. Busch* and *R. Schmidt*, J. prakt. Chem. *131*, 182 (1931).

[91] *W. R. McBride*, *W. G. Finnegan*, and *R. A. Henry*, J. org. Chemistry *22*, 152 (1957).

E. Pyrimidines

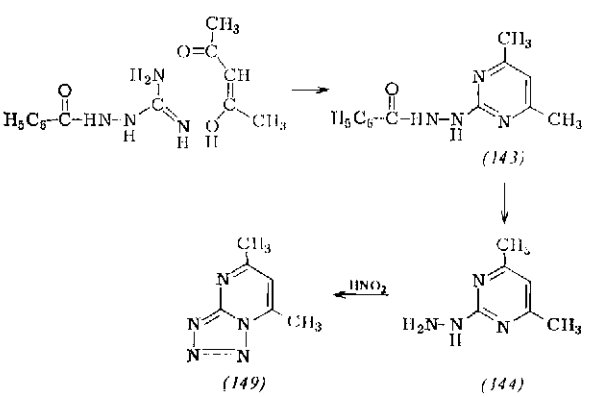
Thiele [92] realized that because it contains a formamidino group, aminoguanidine could be utilized in pyrimidine synthesis provided the hydrazino group be suitably blocked. The obvious method of protecting this group, *viz.* by hydrazone formation [5], was utilized by *Shiho* and *Kanai* [93], who condensed benzylideneaminoguanidine with formylacetone to give 2-benzylidenehydrazino-4-methylpyrimidine *(141)*. This was hydrolysed, albeit in poor yield, to the free hydrazine *(142)* by dilute hydrochloric acid at 80 °C in 5 hours. The structure of *(142)* was confirmed by its preparation from 2-chloro-4-methylpyrimidine and hydrazine hydrate.



(141)

(142)

Alternatively, the hydrazino group in aminoguanidine may be blocked by acylation. Thus, condensation of benzamidoguanidine with acetylacetone [96] yields the benzoyl derivative *(143)* of 2-hydrazino-4,6-dimethylpyrimidine, which can be converted into the free hydrazine *(144)* by hydrolysis.



(143)

(149) *(144)*

A second product, m.p. 165 °C, was isolated from the mother liquors and was formulated [96] as 2-phenyl-5,7-dimethyltriazolo[2,3-*a*]pyrimidine *(145)*; this was thought to have arisen by the alternative condensation *via (146)*. The same compound *(145)* was obtained by refluxing acetylacetone and 3-amino-5-phenyl-1,2,4-triazole *(147)* in ethanol containing pyridine [96]. This synthesis does not, as the authors believed,

[92] *J. Thiele* and *R. Biehan*, Liebigs Ann. Chem. *302*, 299 (1898).

[93] *D. Shiho* and *T. Kanai*, J. chem. Soc. Japan, Pure Chem. Sect. *73*, 862 (1952); Chem. Abstr. *48*, 2070 (1954).

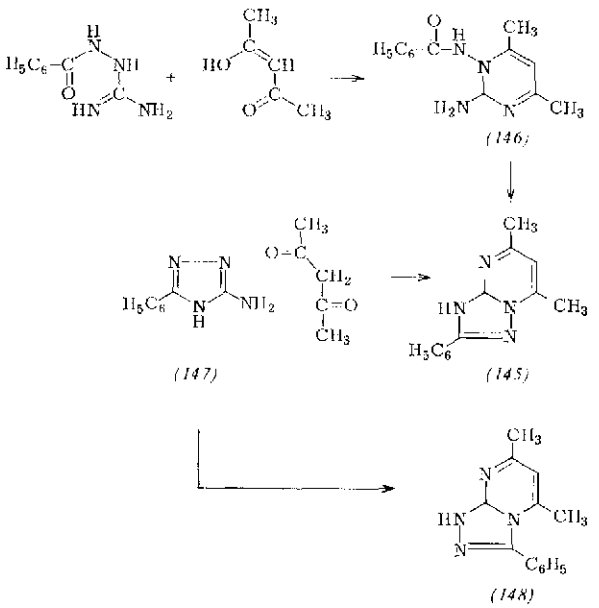
[94] *D. Shiho* and *N. Takahayashi*, J. pharm. Soc. Japan *75*, 773 (1955); Chem. Abstr. *50*, 4976 (1956).

[95] *A. Vystrcil* and *J. Vidlicka*, Chem. Listy *45*, 407 (1951); Chem. Abstr. *46*, 7567 (1954).

[96] *R. Giuliano* and *G. Leonardi*, Il Farmaco (Pavia), Ed. Sci. *11*, 389 (1956).

constitute a structural proof, because there is an equally possible condensation to *(148)*. This second formulation does in fact appear more likely since *(148)* could then be formed simply by the dehydrative cyclization of *(143)*.

Treatment of *(144)* with nitrous acid in dilute acetic acid solution gave the interesting dicyclic compound 5,7-dimethyltetrazolo[2,3-*a*]pyrimidine *(149)*.



An aminoguanidine derivative of pyrimidine was prepared by *Shiho* and *Takahayashi* [94], who converted 2-amino-4-chloro-6-methylpyrimidine by treatment with hydrazine hydrate into the 4-hydrazino-derivative, which on condensation with cyanamide gave 1-(2-amino-6-methylpyrimidin-4-yl)aminoguanidine. Another pyrimidine incorporating the aminoguanidine skeleton was prepared by treating 2-ethylthio-6-methoxy-4-methylpyrimidine with hydrazine hydrate [95].

F. 1,2,4-Triazines

Aminoguanidine, incorporating a chain of one carbon and three nitrogen atoms, is a suitable starting material in the synthesis of 3-amino-1,2,4-triazines, many of which have been obtained by condensing aminoguanidine with bifunctional carbonyl compounds. The use of *o*-quinones in this reaction has proved particularly useful for the preparation of compounds containing a triazine ring fused onto another aromatic system.

I. Synthesis of 1,2,4-Triazines from Aminoguanidine

1. *With Halogenated Carbonyl Compounds*

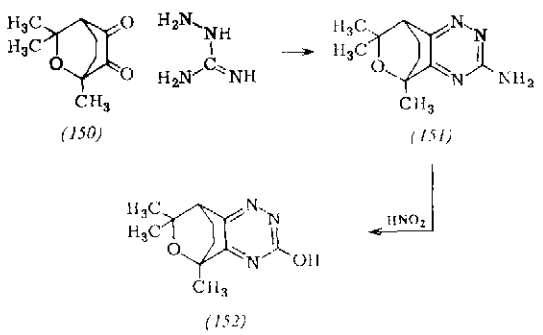
In general, it has not proved possible to obtain 3-amino-1,2,4-triazines by the action of halogenated carbonyl compounds on aminoguanidine. *Thiele* and *Dralle* [4] were the first to show that chloral and aminoguanidine did not give the desired six-membered ring, but merely the unstable guanylhydrazone of chloral, which was converted hydrolytically into the guanylhydrazone of glyoxylic acid. Similarly, monochloroacetaldehyde gave glyoxal diguanylhydrazone [4]. Recently [59], attempted cyclizations of guanyl- and nitroguanylhydrazones of α-halogenoacetophenones again gave either triazoles or eight-membered ring compounds instead of the required triazines.

2. *With Dicarbonyl Compounds*

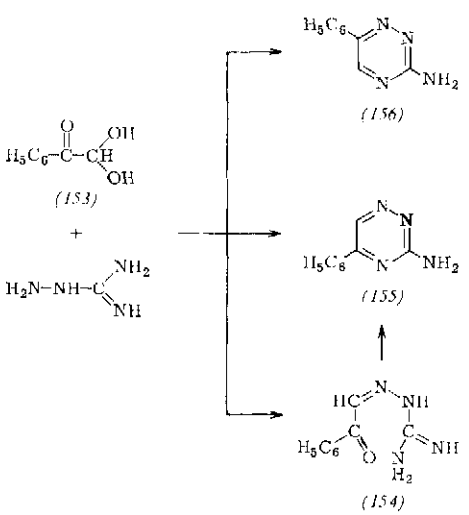
Thiele and *Dralle* [4] were also unsuccessful in their attempts to prepare aminotriazines from aminoguanidine and aliphatic dicarbonyl compounds (*e.g.* glyoxal or diacetyl): osazone-like compounds incorporating two molecules of aminoguanidine and one of the carbonyl compound were isolated.

However, a recent patent [97] describes the synthesis of a large number of triazines from aminoguanidine and aliphatic dicarbonyl compounds including acids such as pyruvic, glyoxylic, or oxalic acids. In a typical example, cyclohexenedione in ethanol is added to aqueous aminoguanidine, with simultaneous addition of a solution of sodium hydroxide to maintain the pH at about 8. The resulting 3-amino-5,6,7,8-tetrahydro-1,2,4-benzotriazine separates out on chilling.

Erickson [98] has described an elegant method of preparing aminotriazines by addition of aliphatic dicarbonyl compounds onto aqueous suspensions of aminoguanidine bicarbonate. Since the latter is only slightly soluble, the solution contains a very low concentration of aminoguanidine and cyclization proceeds faster than osazone formation.



The bicyclic ketone dioxocineole *(150)* reacts with aminoguanidine to yield a monoguanylhydrazone, which is cyclized to an aminotriazole by alkali [99]. Because of steric hindrance around the carbonyl group adjacent to the methyl group, the hydrazino group probably attacks at the alternative carbonyl group. If so, the cyclized product is to be formulated as *(151)*.



[97] Brit. Pat. 755036, Merck & Co. Inc.; Chem. Abstr. *51*, 8151 (1957).

[98] *J. G. Erickson*, J. Amer. chem. Soc. *74*, 4706 (1952); U.S.-Pat. 2653933; Chem. Abstr. *48*, 12815 (1954).

[99] *G. Cusmano*, Anales real. acad. farm. *9*, 307 (1943); Chem. Abstr. *43*, 7926 (1949).

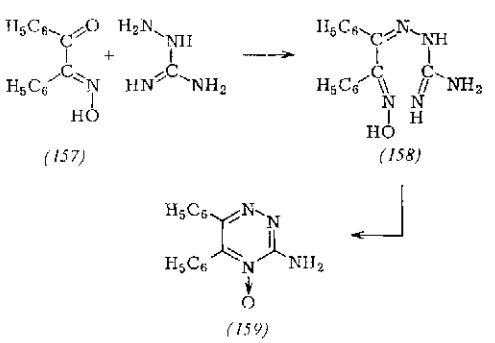
Nitrous acid converts this amine into the corresponding hydroxy compound *(152)*, which is also obtainable from dioxocineole and semicarbazide [99].

Depending on the conditions used, reaction between aminoguanidine and phenylglyoxal hydrate *(153)* yields three different products [100]. In acid media, an intermediate, presumably the monoguanylhydrazone *(154)* is isolated, which can be dehydrated pyrolytically to 3-amino-5-phenyl-1,2,4 triazine *(155)*. This amine, which also results in lower yield on addition of 30 % sodium hydroxide to a suspension of aminoguanidine bicarbonate in boiling phenylglyoxal hydrate, is converted by nitrous acid or boiling potassium hydroxide solution into 3-hydroxy-5-phenyl-1,2,4-triazine.

A second product, thought to be 3-amino-6-phenyl-1,2,4-triazine *(156)* was obtained in 30 % yield on mixing aqueous solutions of aminoguanidine hydrochloride and phenylglyoxal followed by slow basification with excess aqueous potassium hydroxide solution.

Addition of aqueous aminoguanidine hydrochloride to a strongly alkaline solution of *(153)* affords a third product, which is formulated as the imino form of 3- amino-6-phenyl-1,2,4-triazine *(156)* [100]. However, the existence of a separate stable imino-form would appear unlikely, particularly as the two compounds form distinct hydrochlorides and acetyl derivatives.

Reaction between benzil and aminoguanidine gives 3-amino-5,6-diphenyl-1,2,4-triazine [92]. Benzil monoxime *(157)* forms a guanylhydrazone *(158)* [5], the nitrate of which is cyclized in acetic acid to 3-amino-5,6-diphenyl-1,2,4-triazine-*N*-4-oxide *(159)*.

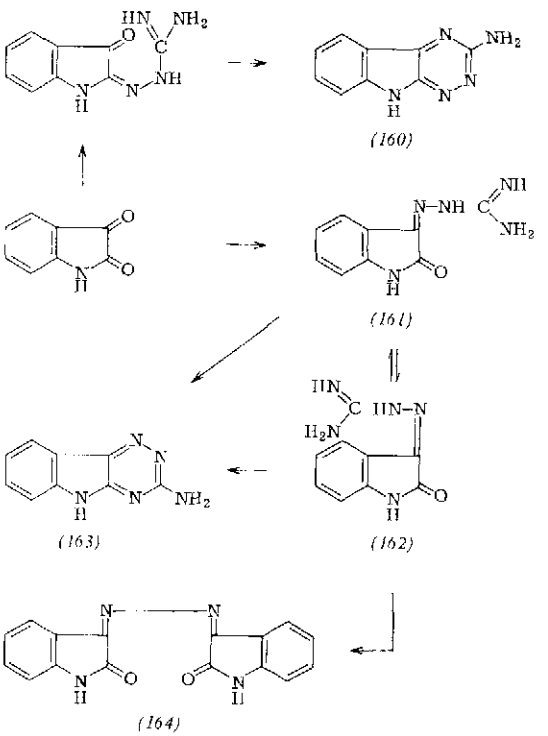


(157) *(158)* *(159)*

Since either carbonyl group of a dicarbonyl compound may undergo the initial condensation with the hydrazino group of aminoguanidine, it is often difficult to assign structures to the resulting triazines.

De [101] condensed isatin with aminoguanidine and formulated the product obtained as *(160)*; he then assigned structures analogous to *(160)* to a series of dyestuffs prepared from substituted indoles [102]. *Rajagopalan* [103] repeated the condensation of isatin in acetic acid. His product, which differed in melting point from that of *De*, had the correct nitrogen content, but the yield was 122 % when calculated from his figures.

This anomaly was cleared up by *King* and *Wright* [104]; on the basis of other evidence for the greater reactivity of the β-carbonyl group in isatin, they suggested that β-guanylhydrazones would be formed preferentially in the initial condensation. By *Rajagopalan*'s procedure, they obtained a base which was shown to be isatin *syn*-β-guanylhydrazone *(161)*. As this material was difficult to crystallize, it was converted into its hydrochloride. Basification of this hydrochloride at 80 °C gave a second crystalline isomeric base, which formed a nitrate and hydrochloride distinct from those of the original base; it was regarded as isatin *anti*-β-guanylhydrazone *(162)*. Boiling 16 % hydrochloric acid reconverted the *anti*-hydrochloride into the *syn*-form. Comparison with relevant compounds suggested that *Rajagopalan* had actually prepared the crude *syn*-β-guanylhydrazone of isatin and not the tricyclic compound claimed [104].



(160) *(161)* *(162)* *(163)* *(164)*

Evidence supporting the assigned configurations was obtained from the observation that the hydrochloride of the *syn*-form was readily cyclized to a triazine *(163)* by boiling for several hours with dilute ammonium hydroxide, whereas the *anti*-form required heating to 250 °C under reduced pressure before undergoing cyclization. A parallel series of guanylhydrazones of *N*-methylisatin was cyclized in a similar manner, yielding the 5-methyl derivative of the tricyclic compound [104].

Acetylation of the *anti*-β-guanylhydrazones gave a mono- and diacetyl derivatives. The latter underwent an interesting transformation on boiling with 16 % hydrochloric acid, being converted into di-isatin azine *(164)* and not into the *syn*-form [104].

3. *With Quinones*

Thiele and *Dralle* [4] condensed α-nitroso-β-napbthol *(165)* with aminoguanidine nitrate and obtained α-oximo-β-naphthylideneaminoguanidine nitrate *(166)*, which cyclized in hot

[100] *J. B. Ekely, R. E. Carlson*, and *A. R. Ronzio*, Rec. Trav. chim. Pays-Bas *59*, 496 (1940).

[101] *S. C. De*, J. Indian chem. Soc. *4*, 183 (1927).

[102] *S. C. De* and *P. C. Dutta*, Ber. dtsch. chem. Ges. *64*, 2604 (1931).

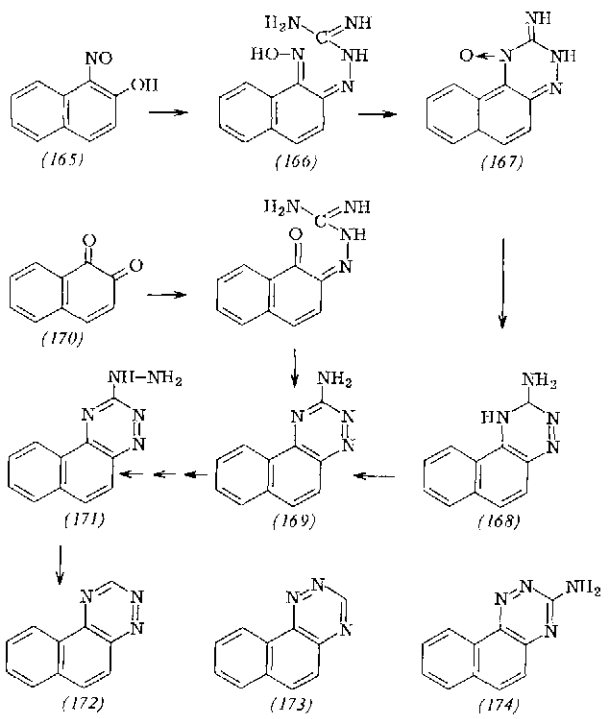
[103] *S. Rajagopalan*, Proc. Indian Acad. Sci. *18A*, 100 (1943).

[104] *H. King* and *J. Wright*, J. Chem. Soc. (London) *1948*, 2314.

aqueous solution to an iminotriazine-*N*-oxide of probable structure *(167)*. Reduction of this compound gave an intermediate *(168)*, which was converted by gentle oxidation into an aminotriazine, m.p. 200–201 °C. This product, which was probably 2-aminonaphtho[1,2]-*as*-triazine *(169)*, was almost certainly obtained by *De* [101] on condensing aminoguanidine with β-naphthoquinone *(170)* in the presence of acetic acid, although he reported the m.p. as 240 °C.

Two groups of workers have recently reexamined these reactions. *Scott* and *Reilly* [105] confirmed the structure assigned to the iminotriazine-*N*-oxide *(167)* by *Thiele* and *Dralle* and demonstrated its amphoteric nature by preparing both metal salts and the salts of organic acids including the picrate. On treating *(167)* with phenyl isocyanate, a urea derivative was obtained. The results of the reduction of the iminotriazine-*N*-oxide *(167)*, and the oxidation of the resulting intermediate *(168)* were confirmed; the final product was again an aminotriazine *(169)*, m.p. 201 °C. Condensation of the 1 *O*-methyloxime of 1,2-naphthoquinone with aminoguanidine gave the *O*-methyl derivative of *(166)*, which was stable towards boiling water.

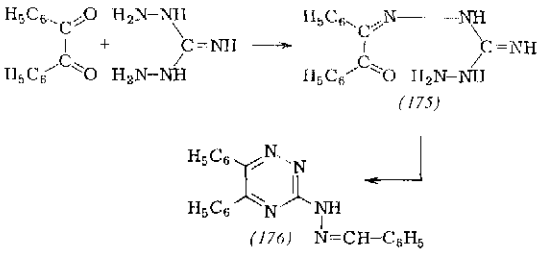
Fusco and *Bianchetti* [106] attempted to account for the difference in the melting points reported for *(169)* by *De* and by *Thiele* and *Dralle*. The two unsubstituted naphthotriazines *(172)* and *(173)* had been prepared previously [106];



when *De*'s aminotriazine was degraded *via* the hydrazine *(171)*, the parent compound *(172)* was obtained. *De*'s compound must therefore be *(169)*. As *De* might possibly have obtained a mixture of the two isomeric aminotriazines *(169)* and *(174)*, the latter was synthetized separately. A mixture of the two isomers melted at 180–190 °C, however; it therefore appears that the melting point reported by *De* is either an error or a misprint.

II. Synthesis of 1,2,4-Triazines from Diaminoguanidine

On condensing benzil with diaminoguanidine nitrate, *Lieber* and *Strojny* [107] did not obtain the expected seven-membered heterocyclic compound; instead, benzil mono(aminoguanyl)hydrazone *(175)* was the main product (85 %), and was still obtained when diaminoguanidine was employed in twofold excess.



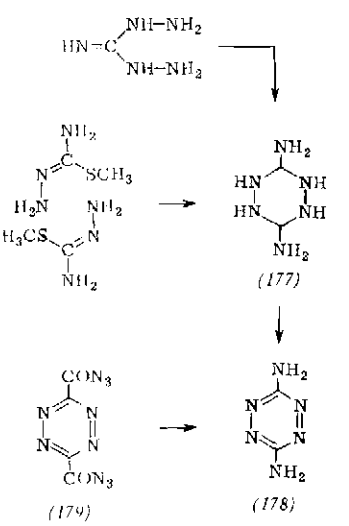
Further reaction of *(175)* with benzaldehyde afforded 3-benzylidenehydrazino-5,6-diphenyl-1,2,4-triazine *(176)* in 19 % yield [107].

G. Tetrazines

Aminoguanidine has so far not been used extensively for the synthesis of tetrazines, but such compounds have been isolated on several occasions from reactions involving aminoguanidine or designed to produce aminoguanidine derivatives.

In 1913, *Ponzio* and *Gastaldi* [108] isolated a violet solid by treating aminoguanidine with aqueous potassium hydroxide. They formulated this compound, on rather inadequate evidence, as 3,6-diamino-1,2,4,5-tetrazine. This work was later discussed by *Lieber* and *Smith* [2].

More recently, *Scott* and *Reilly* [5] found that, on treatment with various organic bases, *S*-methylisothiosemicarbazide yields a dark-red compound, m.p. 360 °C, which was formulated as 3,6-diamino-1,2,4,5-tetrazine *(178)*. The initial reaction product is presumably the dihydrotetrazine *(177)*, which is oxidized in air to the tetrazine. This compound *(178)* was not identical with *Ponzio* and *Gastaldi*'s product. Confirmation of the structure *(178)* assigned by *Scott* and *Reilly* was provided by *Lieber* and co-workers [109], who synthetized *(178)* unequivocally from authentic 3,6-dicarboxy-1,2-di-



[105] *F. L. Scott* and *J. Reilly*, Nature (London) *169*, 584 (1952).

[106] *R. Fusco* and *G. Bianchetti*, Gazz. chim. ital. *87*, 438, 446 (1957).

[107] *E. Lieber* and *E. J. Strojny*, J. org. Chemistry *17*, 518 (1952).

[108] *G. Ponzio* and *C. Gastaldi*, Gazz. chim. ital., *43*, II, 129 (1913); ibid. *44*, I, 257, 277 (1914); ibid., *45*, I, 181 (1915).

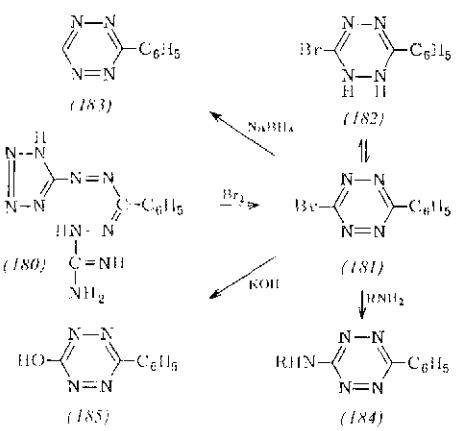
[109] *C. H. Lin*, *E. Lieber*, and *J. P. Horwitz*, J. Amer. chem. Soc. *76*, 427 (1954).

hydro-1,2,4,5-tetrazine, *via* the 3,6-dicarbonyl azide *(179)*, in 11 % overall yield. Suitable treatment of diaminoguanidine with nitrous acid gave an intermediate which was oxidized to the same diaminotetrazine *(178)* [109].

Diaminotetrazine is easily reduced and the reduced material readily reoxidized to the parent compound, a behaviour that is characteristic of tetrazines [109]. The aromatic nature of the tetrazine ring was illustrated by the ease of diazotization of both amino groups; the resulting bis-diazonium salt was coupled with β-naphthol to form a dye [109].

A 1,4-disubstituted 3,6-diaminotetrazine was obtained by *Scott* [110] by the action of bases on *S*-methyl-(or ethyl)-1-phenylisothiosemicarbazide.

Grakauskas, *Tomasewski*, and *Horwitz* [89] isolated a dark-red solid of composition $C_8H_5N_4Br$ by oxidizing 1-guanyl-3-phenyl-5-(tetrazol-5-yl)formazan *(180)* with bromine in glacial acetic acid solution at 40–60 °C. This compound was easily reduced with zinc dust to a pale yellow solid $C_8H_7N_4Br$ (*i.e.* containing two more atoms of hydrogen), which is reoxidized by bromine to the original product. More vigorous reduction of the red compound $C_8H_5N_4Br$ with sodium borohydride, followed by gentle oxidation with sodium nitrite gave the known compound 3-phenyl-1,2,4,5-tetrazine *(183)*. These results suggest that the red material was 3-bromo-6-phenyl-1,2,4,5-tetrazine *(181)*.

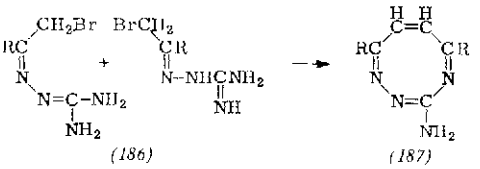


(183) *(182)* *(180)* *(181)* *(185)* *(184)*

The bromine atom in *(181)* proved to be readily displaceable by a number of reagents. Treatment with potassium hydroxide gave 3-hydroxy-6-phenyl-1,2,4,5-tetrazine *(185)*, whilst reaction with a number of amines gave a series of *N*-substituted 3-amino compounds *(184)* [89].

H. Eight-Membered Heterocyclics

Beyer and *Pyl* [111] found that ω-bromoacetophenone reacts with aminoguanidine in alcoholic hydrobromic acid to form the hydrobromide of ω-bromoacetophenone guanylhydrazone, m.p. 198 °C *(186)*. Under the influence of weak bases, *e.g.* sodium acetate or ammonia, two molecules of the hydrazone condensed at

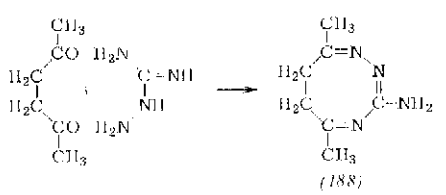


(186) *(187)*

room temperature, with loss of two molecules of hydrogen bromide and one of aminoguanidine, to form 3-amino-5,8-diphenyl-1,2,4-triazacyclooctatetraene *(187)* as orange brown prisms, m.p. 208 °C (decomp.), in 37–44 % yield. Similar heterocyclic compounds were prepared from *p*-chloro-, *p*-bromo-, and *m*-nitro-ω-bromoacetophenone [111].

Since dibenzoylethylene had been prepared by treating ω-bromoacetophenone with alcoholic potassium hydroxide [112], it appeared that the initial stage of the reaction might entail formation of dibenzoylethylene diguanylhydrazone, which then cyclized by elimination of one molecule of aminoguanidine. However, the diguanylhydrazone of either *cis*- or *trans*-dibenzoylethylene failed to cyclize under the conditions of the reaction, and a different mechanism must therefore be operative.

The carbon-carbon double bond in *(187)* adds on a molecule of bromine and then loses hydrogen bromide to form a monobromo derivative of *(187)*. The 3-amino group exhibits normal properties as was shown by the formation of salts (*e.g.* hydrochloride, hydrobromide) and acyl derivatives (*e.g.* acetyl and benzoyl). Treatment with phenyl isothiocyanate formed the appropriate phenylthiourea. An imino form of *(187)* also appears to exist; a crystalline nitroso compound which is soluble in both acids and alkalis was obtained by reaction with isoamyl nitrite. When *(187)* was oxidized with hydrogen peroxide or potassium permanganate, two molecules linked together to form 3,3′-azo-bis-1,2,4-triaza-5,8-diphenylcyclooctatetraene [111].



(188)

A precedent for this type of large-ring formation is the synthesis of 1,2,4-triaza-3-amino-5,8-dimethyl-2,4,8-cyclooctatriene *(188)* by reaction of aminoguanidine with diacetylethane [4].

Received, September 25th, 1962 [A 292/96 IE]
German version: Angew. Chem., to appear in December.

[110] *F. L. Scott*, Chem. and Ind. *1954*, 158.

[111] *H. Beyer* and *T. Pyl*, Angew. Chem. *68*, 374 (1956); Liebigs Ann. Chem. *605*, 50 (1957).

[112] *B. M. Bogoslowski*, Zh. Obsh. Khim. *14*, 993 (1944).

Synthesis of Substituted Acetylenic Compounds

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The preparation of the ynamine *(1)* in 86 % yield opens not only the way to this otherwise rather inaccessible class of compounds [2], but also offers a general method for the synthesis of mono- and disubstituted acetylenic compounds.

$$C_6H_5CH{=}CClF \xrightarrow[\text{10 min at } -80\,^\circ C,\ \text{30 min at } -20\,^\circ C]{2\,LiN(C_2H_5)_2 \text{ in ether}} C_6H_5C{\equiv}C{-}N(C_2H_5)_2 \quad (1)$$

The elemental analysis and the infrared spectrum establish structure *(1)* in agreement with the results of [2].

By means of this reaction, which is the result of previous findings [1], we succeeded in preparing a number of other heterosubstituted acetylenes. The indicated yields are derived from preliminary experiments and may be open to improvement.

(a) $R'CH{=}CXF + 2\,RM \rightarrow R'{-}C{\equiv}C{-}R + (RH + MX + MF)$
M = alkali metal or the like, X = halogen

Examples:

$$C_6H_5{-}CH{=}CClF \xrightarrow{2\,Li\text{-}n\text{-}butyl} C_6H_5{-}C{=}C{-}C_4H_9 + \text{allenic isomer, yield } ca.\ 20\,\%$$

$$C_6H_5{-}CH{=}CClF \xrightarrow[2\,KOC(CH_3)_3]{} C_6H_5{-}C{\equiv}C{-}OC(CH_3)_3, \text{ yield } ca.\ 50\,\%$$

Phenyl- and methyl-lithium gave analogous reactions with low yields.

$$HCH{=}CClF \xrightarrow{2\,KOC(CH_3)_3} HC{\equiv}C{-}OC(CH_3)_3, \text{ yield } ca.\ 20\,\%$$

(b) $R'CX{=}CXF + 2\,RM \rightarrow R'{-}C{\equiv}C{-}R + (RX + MX + MF)$

Examples:

$$C_6H_5CBr{=}CClF \xrightarrow{2\,LiC_6H_5} C_6H_5{-}C{\equiv}C{-}C_6H_5, \text{ yield } ca.\ 70\,\%$$

Phenylmagnesium bromide gives only traces of tolane, whereas phenyl- and methyl-lithium react well.

$$FCCl{=}CClF \xrightarrow{3\,LiC_6H_5} C_6H_5{-}C{\equiv}C{-}C_6H_5, \text{ yield } ca.\ 30\,\%, \text{ cf. [3]}$$

Received, Jan. 2nd, 1963 [Z 519/352 IE]
Publication withheld until now at the author's request
German version: Angew. Chem. 75, 638 (1963).

[1] Communication No. V on Heterosubstituted Acetylenes; Communication No. IV: *H. G. Viehe* and *E. Franchimont*, Chem. Ber. *95*, 319 (1962).

[2] *V. Wolf* and *F. Kowitz*, Liebigs Ann. Chem. *638*, 33 (1960).

[3] *D. Seyferth*, *D. E. Welch* and *G. Raab*,, J. Amer. chem. Soc. *84*, 4267 (1962).

Lithium Phthalocyaninatomanganate(I) and (0)

By Dr. R. Taube and cand. chem. H. Munke

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der Universität Greifswald (Germany)

Manganese phthalocyanine (MnPc) and a solution of dilithiobenzophenone (Li_2Bzph) in tetrahydrofuran (THF) react together on exclusion of oxygen and moisture according to the scheme below to give *(1)* and *(2)* as bright and dark green crystals, respectively.

$$MnPc + Li_2Bzph \xrightarrow{THF} Li[MnPc]{\cdot}6THF + LiBzph \quad (1)$$

$$Li[MnPc]{\cdot}6THF + Li_2Bzph \xrightarrow{THF} Li_2[MnPc]{\cdot}6THF + LiBzph \quad (2)$$

On thermal degradation *in vacuo*, they both liberate tetrahydrofuran quantitatively; in air, they decompose immediately with darkening in color and evolution of tetrahydrofuran. In addition to their solubility in tetrahydrofuran, the two compounds also dissolve in acetonitrile, giving intensely violet solutions. Iodine in tetrahydrofuran oxidizes them quantitatively to LiI and MnPcI. The ionic nature of *(1)* and *(2)* was established by transport experiments in acetonitrile. Their magnetic moments, measured at 293 °K, were $\mu_{eff.} = 2.86$ Bohr magnetons corresponding to two unpaired electrons for *(1)*, and $\mu_{eff.} = 4.13$ Bohr magnetons corresponding to three unpaired electrons for *(2)*, thus confirming the even and odd total number of electrons to be expected for one- or two-stage reduction of MnPc. Formally one can ascribe the oxidation numbers +1 and 0, respectively, to the central manganese atoms in *(1)* and *(2)*.

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German version: Angew. Chem 75, 639 (1963).

Photoisomerisation of 1,3-Cyclohexadienes

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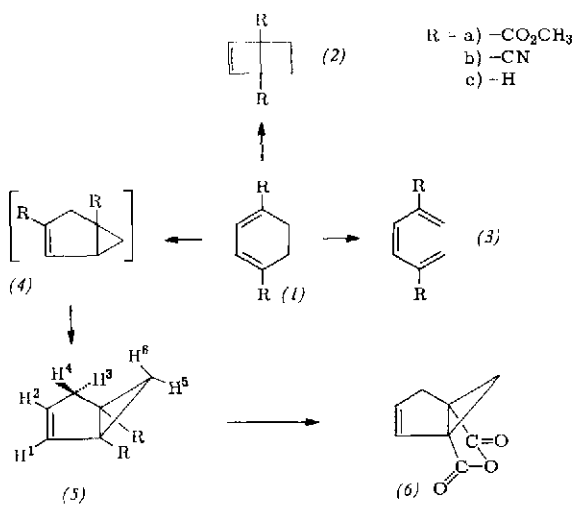
(Germany)

Diazomethane-sensitized intramolecular photoisomerisation of dimethyl 1,3-cyclohexadiene-1,4 dicarboxylate *(1a)* to give dimethyl bicyclo[2.2.0]hex-2-ene-1,4-dicarboxylate *(2a)* [1] is not limited by the specific geometrical or optical properties of the ester groups. Under the same conditions, irradiation of a solution in ether of the dinitrile *(1b)* (λ_{max} in ethanol = 306 mμ, ε = 11100; 296 mμ, ε = 11150; proton magnetic resonance spectrum: singlets at τ = 3.25, 2 protons and τ = 7.45, 4 protons) in the presence of diazomethane gives bicyclo[2.2.0]hex-2-ene-1,4 dicarbonitrile *(2b)*, in about 70 % yield as a colorless oil, b.p. 90–91 °C/0.001 mm, only terminal absorption at 220 mμ; proton magnetic resonance spectrum: singlet at τ = 4.63 and a A_2B_2-multiplet at τ = 8.57; in the infrared spectrum, δ (=C–H) of cyclobutene lies



at 741 cm^{-1} [2]). However, *(1a)* and *(1b)* behave differently on unsensitized irradiation (Hanau Q 81 high-pressure mercury lamp). Compound *(1b)* undergoes ring opening to give

the hexatriene *(3b)* (λ_{max} = 260, 252, 247 mμ), which is stable only in solution, but *(1a)* affords a sterically non-uniform dimer (m.p. 184–189 °C) and about 20–25 % yield of a monomeric photo-product, to which we assign the structure of dimethyl bicyclo[3.1.0]hex-2-ene-1,5-dicarboxylate *(5a)* (only terminal absorption at 220 mμ, ε = 1700, cyclopropane ring deformation band at 1020 cm^{-1}, PMR spectrum: H-1, H-2, H-3, and H-4 two triplets each at τ = 3.98; 4.07 to 4.42; 4.51–6.61; 6.90–7.40; 7.69; J_{12} = 6.0 c.p.s.; $J_{13} \simeq J_{23} \simeq J_{14} \simeq J_{24} \simeq$ 1.9 c.p.s.; for H-5 and H-6 a doublet each at τ = 7.58 and 9.18; J = 4.0 c.p.s.; and the H_3CO singlet at τ = 6.33). The diester *(5a)* can be converted into the dicarboxylic acid and the tricyclic anhydride *(6)*. Irradiation of *(1a)* under conditions which preclude excitation of the chromophoric system in *(4a)* has so far produced no evidence for the occurrence of *(4a)* as an intermediate [3]. We must assume that the rearrangement of the excited state of *(1a)* to *(5a)* occurs directly. It is significant that diazomethane is inactive as a sensitizer for valence isomerisation of unsubstituted 1,3-cyclohexadiene *(1a)*. As in the unsensitized irradiation, the ring of *(1c)* is opened to give 1,3,5-hexatriene *(3c)* [4]. Possibly activation of the double bonds in 1,3-cyclohexadiene by electronegative substituents is a prerequisite for the sensitizing action of diazomethane.

Received, May 16th, 1963 [Z 509/340 IE]
German version: Angew. Chem. *75*, 639 (1963).

[1] *H. Prinzbach* and *J. H. Hartenstein*, Angew. Chem. *74*, 651 (1962); Angew. Chem. internat. Edit. *1*, 507 (1962).

[2] *W. G. Dauben* and *R. L. Cargill*, Tetrahedron *12*, 186 (1961).

[3] *H. Prinzbach* and *H. Hagemann*, unpublished work.

[4] *D. H. R. Barton*, Helv. chim. Acta *42*, 2604 (1959); *R. J. deKock*, *N. G. Minnaard*, and *E. Havinga*, Rec. Trav. Chim. Pays-Bas *79*, 922 (1960).

Duroquinone-Cyclopentadienyl-Cobalt [1]

By Priv.-Doz. Dr. G. N. Schrauzer and Dr. H. Thyret

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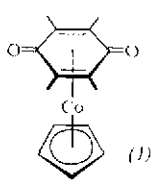
On heating duroquinone with cyclopentadienylcobalt dicarbonyl for several hours at 120 °C in a high-boiling solvent, diamagnetic, red-brown duroquinone-cyclopentadienyl-cobalt *(1)* (decomp. 275 °C) is formed; this is the first π-complex of this transition metal with a quinone [2]. The compound is very polar, hygroscopic, can be sublimed *in vacuo*, is only sparingly soluble in the usual organic solvents, but is readily soluble in water. Its proton magnetic resonance spectra show only two sharp signals, in $CHCl_3$ at 4.86 and 2.20 ppm, in H_2O at 5.10 and 2.12 ppm (at 60 Mc/s with tetramethylsilane as external standard), with an intensity ratio of 5:12. The carbonyl groups of *(1)* are protonated in strong acids; in



(1)

conc. H_2SO_4, the proton resonance signals occur at 6.02 and 2.72 ppm. The carbonyl absorption in the infrared of the duroquinone complex in KBr is split into two bands at 1563 and 1536 cm^{-1} (cf. duroquinone, 1629 cm^{-1}; bis-duroquinone-nickel(0), 1577 cm^{-1}; duroquinone-1,5-cyclooctadienyl-nickel, 1553 cm^{-1} [3]). This marked shift to longer wavelengths indicates significant interaction between the $2b_{2g}$-MO of the duroquinone and a suitable 3d/4p-orbital of the cobalt atom.

Besides further duroquinone absorption bands, the characteristic bands of the symmetrical C_5H_5-residue at 3086, 1433, 1124, 1026, 836/830 (doublet) cm^{-1} (KBr) are observed. The absorption spectrum in the visible and ultraviolet regions ($CHCl_3$ solution) contains the following bands: 460 (700); 388 (5000); 312 (8500); 250 (12000) mμ (mol. extinction coefficient in brackets). Application of MO-theory leads to a term-level scheme indicated in Fig. 1 which shows the predicted stabilization of the b_{3g} and $2b_{1u}$ duroquinone MO's due to the interaction with the metal orbitals (cf. [1b]). In water, a further band at 226 mμ (13000), which we have tentatively assigned to a 3d-π* (C_5H_5) transition, is observed. The characteristic color of *(1)* is largely due to the

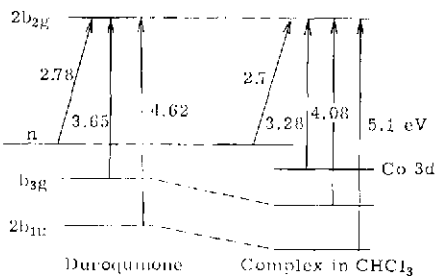


Fig. 1. Transitions in duroquinone and duroquinone-cyclopentadienyl-cobalt (in $CHCl_3$).

band at 460 mμ (corresponding to the π-$2b_{2g}$-transition in free duroquinone) and the band in the visible range at 388 mμ (charge-transfer transition). The high stability of *(1)* in comparison to that of olefin-duroquinone-nickel complexes is largely attributable to the fact that the latter compounds contain two electrons in an antibonding orbital, whereas in *(1)*, all the electrons participating in bonding can be accommodated in bonding, or practically non-bonding orbitals.

Received, May 20th, 1963 [Z 511/338 IE]
German version: Angew. Chem. *75*, 641 (1963).

[1] a) Communication No. 7 on Quinone π-Complexes of Metals.
b) Communication No. 6: *G. N. Schrauzer* and *H. Thyret*, Theoret. chim. Acta (Berlin) *1*, 172 (1963).

[2] Analogous complexes of rhodium and iridium have been prepared in the meantime by another route (experiments with *K. C. Dewhirst*); these will be described in detail elsewhere.

[3] *G. N. Schrauzer* and *H. Thyret*, Z. Naturforschung *17b*, 73 (1962).

Germylsilazanes and Stannylsilazanes

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In dry organic solvents, trialkylchlorogermanes [1] and trialkylchlorostannanes react with 1,1,1,3,3,3-hexamethyldisilazan-2-sodium *(1)* [2] according to the following equation to give good yields of 1,1,1,3,3,3-hexamethyl-2-trimethylgermyldisilazane *(2)*, m.p. 29–32 °C, b.p. 54–56 °C/1 mm; 1,1,1,3,3,3-hexamethyl-2-trimethylstannyldisilazane *(3)*, m.p. 20–22 °C, b.p. 58–59 °C/1 mm; and 1,1,1,3,3,3-hexamethyl-2-tri-n-butylstannyldisilazane *(4)*, b.p. 140–145 °C/1 mm.

$$\underset{(1)}{[(CH_3)_3Si]_2NNa} + ClMR_3 \rightarrow [(CH_3)_3Si]_2N{-}MR_3 + NaCl$$

(2) M = Ge, R = CH_3
(3) M = Sn, R = CH_3
(4) M = Sn, R = n-C_4H_9

Whereas *(2)* forms waxy crystals which are surprisingly stable towards water, *(3)* and *(4)* are rapidly attacked by moisture at the Sn–N bond. The proton magnetic resonance spectra [3] of *(2)* and *(3)* show expected peaks with relative areas of 2:1. The displacement of the asymmetric Si–N(M) frequency to higher wave-numbers relative to that of 1,1,1,3,3,3-hexamethyl-2-trimethylsilylsilazane $[(CH_3)_3Si]_3N$

(5) [4] points to an increase in the double bond character of the bond between silicon and nitrogen [*(5)*: 916, *(2)*: 931, *(4)*: 941, *(3)*: 950 cm^{-1}].

$$(CH_3)_2GeCl_2 + 2\ [(CH_3)_3Si]_2NNa \rightarrow [(CH_3)_3Si]_2N-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{Ge}}}}-N[Si(CH_3)_3]_2 + 2\ NaCl$$

Dichlorodimethylgermane reacts with *(1)* according to the equation to give the corresponding bis(disilazyl)germane (b.p. *ca.* 135 °C/1 mm), albeit only in moderate yields (*ca.* 30–40 %).

Received, May 20th, 1963 [Z 512/345 IE]
German version: Angew. Chem. *75*, 642 (1963).

[1] *M. Schmidt* and *I. Ruidisch*, Z. anorg. allg. Chem. *311*, 331 (1961).

[2] *U. Wannagat* and *H. Niederpruem*, Chem. Ber. *94*, 1540 (1961).

[3] Varian A60 instrument (60 Mc). Measurements made on dilute carbon tetrachloride solutions. Tetramethylsilane as internal standard.

[4] *J. Goubeau* and *J. Jiménez-Barbera*, Z. anorg. allg. Chem. *303*, 217 (1960).

1,1-Diphenyl-1-phosphabenzene [1]

By Dr. G. Märkl

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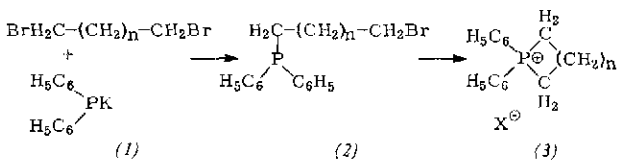
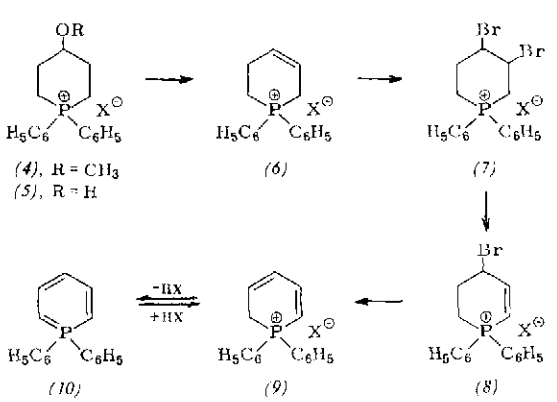
Slow addition of diphenylphosphinopotassium *(1)* [2] in a mixture of dioxan and tetrahydrofuran to a boiling solution of an ω,ω′-dibromoalkane gives the diphenyl-ω-bromoalkylphosphine *(2)*, which at once quaternizes intramolecularly to the cyclic phosphonium salt *(3)*:



(1) *(2)* *(3)*

(3): n = 2, X = $B(C_6H_5)_4^{\ominus}$, m.p. 185–187 °C, 77 % yield; n = 3, X = $Br^{\ominus}$, m.p. 262–263 °C, 49 % yield; n = 4, X = $ClO_4^{\ominus}$, m.p. 208 °C, 36 % yield.

1,5-Dibromo-3-methoxypentane affords 4-methoxy-1,1-diphenyl-1-phosphoniocyclohexane bromide *(4)*, m.p. 220 to 221 °C, 46 % yield, and subsequent demethylation with hydrobromic acid in acetic acid gives the alcohol *(5)*, m.p. 148–149 °C, 58 % yield.



(4), R = CH_3
(5), R = H
(6) *(7)*
(10) *(9)* *(8)*

Compound *(5)* can be dehydrated with potassium hydrogen sulfate at 210–220 °C to give the phosphoniocyclohexene derivative *(6)*, where X = $ClO_4^{\ominus}$, m.p. 177–179 °C, 60 % yield; $\nu_{C=C}$ 1637 cm^{-1}; bromination of *(6)* takes place smoothly in glacial acetic acid to give *(7)*, X = $ClO_4^{\ominus}$, m.p. 206–208 °C, 68 % yield; *(7)* crystallizes from a mixture of acetonitrile and ether with one mole of acetonitrile, m.p. 178–180 °C. The salt *(7)* loses 1 mole of hydrogen bromide in dimethylformamide/quinoline at room temperature to form 4-bromo-1,1-diphenyl-1-phosphoniocyclohex-2-ene perchlorate *(8)*, where X = $ClO_4^{\ominus}$, m.p. 175–176 °C, 88 % yield; *(8)* crystallizes with 1 mole of acetonitrile from a mixture of acetonitrile and ether. $\nu_{C=C}$ 1596 cm^{-1}. The salt *(8)* is dehydrobrominated in hot anhydrous phosphoric acid to the phosphoniocyclohexadiene perchlorate *(9)*, X = $ClO_4^{\ominus}$, m.p. 117–119 °C, $\nu_{C=C}$ 1626, 1572, 1550 cm^{-1}. 1,1-Diphenyl-1-phosphabenzene *(10)* is precipitated from its aqueous solution by dilute sodium hydroxide as an amorphous yellow powder (λ_{max} = 409 mμ in methanol) which is stable in water but reforms the salt *(9)* in acid.

Like the corresponding phosphanaphthalene derivative [1], *(10)* autoxidizes readily in solution, forming red and violet methylenephosphoranes of unclarified structure.

Even in an atmosphere of nitrogen, dehydrobromination of *(8)* or *(9)* with quinoline or diisopropylethylamine [3] in boiling dimethylformamide leads beyond *(10)* to a deep-blue stable methylenephosphorane (λ_{max} = 634 mμ in methanol), in addition to small quantities of red compounds, structural studies of which are in progress.

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German version: Angew. Chem. *75*, 669 (1963).

[1] Communication No. III on Cyclic Methylenephosphoranes; Communication No. II: *G. Märkl*, Angew. Chem. *75*, 168 (1963); Angew. Chem. internat. Edit. *2*, 153 (1963).

[2] *K. Issleib* and *H. O. Fröhlich*, Z. Naturforschg. *14b*, 349 (1959), *K. Issleib* and *A. Tzschach*, Chem. Ber. *92*, 1118 (1959).

[3] *S. Hünig* and *M. Kiessel*, Chem. Ber. *91*, 380 (1958).

Reactions of Di-(α-pyridyl) Carbonate

Reactive Esters of Heterocyclic Alcohols, I

By Dr. W. Kampe

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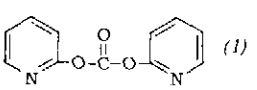
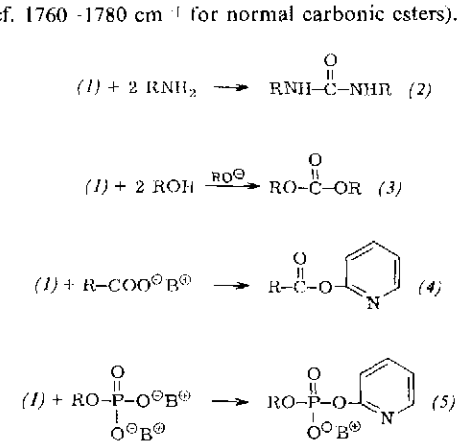
der Technischen Hochschule Darmstadt (Germany)

α-Hydroxypyridine reacts with phosgene in a molar ratio of 4:1 (pyridine can also be used to absorb the HCl formed) at room temperature in dry tetrahydrofuran or benzene to give di-(α-pyridyl) carbonate *(1)* in almost quantitative yield.



(1)

Compound *(1)* is crystalline, m.p. 111–112 °C; it hydrolyses slowly in water at room temperature with evolution of CO_2. Its infrared spectrum contains a carbonyl band shifted to 1796 cm^{-1} (cf. 1760–1780 cm^{-1} for normal carbonic esters).



(1) + 2 RNH_2 → $RNH-\overset{\displaystyle O}{\overset{\|}{C}}-NHR$ *(2)*

(1) + 2 ROH $\xrightarrow{RO^{\ominus}}$ $RO-\overset{\displaystyle O}{\overset{\|}{C}}-OR$ *(3)*

(1) + $R-COO^{\ominus}B^{\oplus}$ → $R-\overset{\displaystyle O}{\overset{\|}{C}}-O-$ *(4)*

(1) + $RO-\overset{\displaystyle O}{\overset{\|}{P}}(O^{\ominus}B^{\oplus})-O^{\ominus}B^{\oplus}$ → $RO-\overset{\displaystyle O}{\overset{\|}{P}}(O^{\ominus}B^{\oplus})-O-$ *(5)*

The reactions of *(1)* usually give high yields [*(2)*, R = C_6H_{11}, 92 % yield; *(3)*, R = C_7H_7, 91 % yield; *(4)*, R = C_6H_5, 85 % yield; *(5)*, R = C_6H_5, 95 % yield]. Further acylations can be

carried out with *(4)* and *(5)*, occasionally under very mild conditions. Furthermore, compounds of type *(5)* are, as far as we know, the first stable examples of so-called imidoyl phosphates, which are assumed to be intermediates in the phosphorylation of carbodiimides, trichloroacetonitrile, cyanuric chloride, *etc.*

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German version: Angew. Chem. 75, 641 (1963).

Isomerism of 1,3,4-Oxadiazolines

By Dr. E. Fahr, K. Döppert, and Dr. F. Scheckenbach

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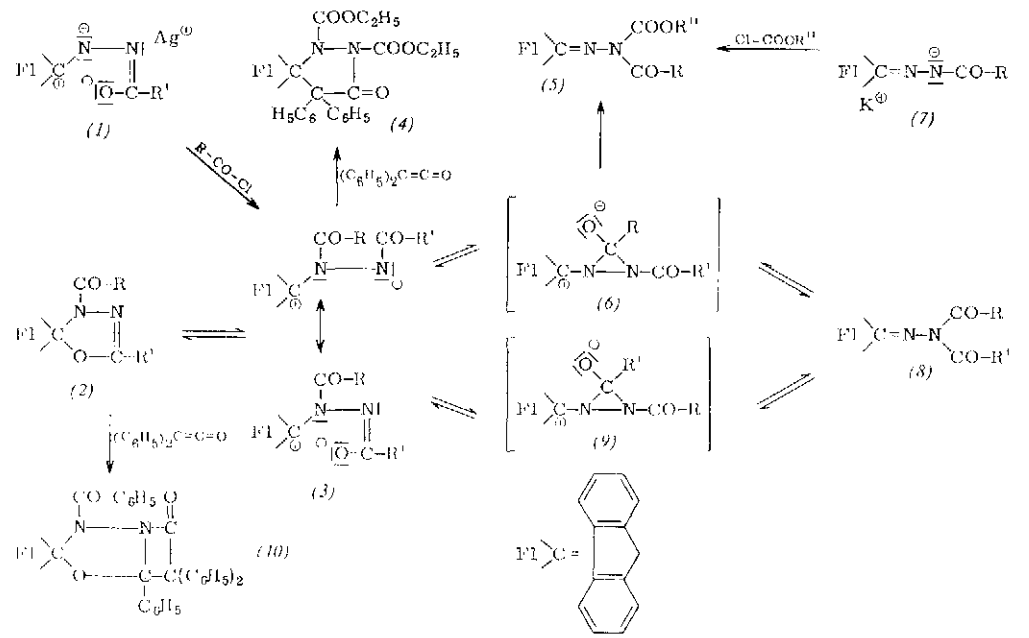
1,3,4-Oxadiazolines *(2)*, which are accessible from diazofluorene and α,α'-dicarbonylazo compounds [1, 2] or by interaction of the silver salts *(1)* and acyl chlorides [3], exhibit a new kind of ring-chain isomerism. Thus, for example, the compounds derived from diazo-fluorene and azodicarboxylic esters are present as oxadiazoles *(2a)* in the solid state, but form an equilibrium in solution (the position of which depends on the dielectric constant of the solvent) between the oxadiazoline *(2a)* and the azomethine-imine *(3a)* isomers [4]. With R'' = C_2H_5 in dichloromethane/n-heptane: isobestic points at 242 and 263 mμ; specific bands in the infrared (CCl_4): oxadiazole form: 5.85 and 5.98 μ; azomethine-imine form: 5.62; 5.74; 6.08 μ. With increasing dielectric constant of the solvent, the position of the equilibrium is displaced towards the azomethine-imine form, which may be trapped, *e.g.* by diphenylketene to yield *(4)*. Above 50 °C, irreversible conversion into the *N'*-acyl-*N'*-alkoxycarbonylhydrazone *(5a)* sets in, proceeding presumably by way of the intermediate *(6)* [5]. The oxadiazolines *(2b)* and *(2c)*, which are accessible from *(1a)* and acetyl chloride and from *(1b)* and ethyl chloroformate, respectively, also rearrange irreversibly into the hydrazone *(5b)* which in turn is obtainable from *(7a)* and ethyl chloroformate.

Isomerisation of *(2d)*, which is obtained from *(1b)* and acetyl chloride, proceeds differently: on warming, it rearranges reversibly via *(3b)* and *(6)* to the hydrazone *(8a)*, which may be itself obtained by the action of acetyl chloride on *(7a)*. At room temperature, *(8a)* reverts slowly into *(2d)*. In the case of *(2e)*, rearrangement proceeds via *(3c)* → *(6)* → *(8b)* → *(9)* → *(3d)* to yield *(2f)*, which does not isomerize, not even in the molten state. Compound *(2e)* is obtainable from *(1b)* and benzoyl chloride, while *(2f)* results from *(1c)* and acetyl chloride. The hydrazone *(8b)* is so labile that it rearranges immediately to *(2f)* when its preparation from *(7b)* and acetyl chloride is attempted. The oxadiazoline *(2g)* is very stable, and even in the melt yields only limited amounts of the azomethine-imine form *(3a)*. Diphenylketene adds onto *(2g)* to afford *(10)*, from which *(2g)* is regenerated on treatment with alkali.

The reason for the differing behavior of the silver and potassium salts of the monoacylhydrazones on acylation is revealed by infrared spectroscopic examination of these salts. The silver salt is present in the lactim structure *(1)* – indicated by the absence of carbonyl valence vibration bands [6] – while the potassium salt has structure *(7)*, for the position of the carbonyl valence vibration band is the same as for the free monoacylhydrazones.



(1a): R' = OC_2H_5; *(1b)*: R' = CH_3; *(1c)*: R' = C_6H_5;
(2a): R = R' = OR''; *(2b)*: R = CH_3, R' = OC_2H_5; *(2c)*: R = OC_2H_5, R' = CH_3; *(2d)*: R = R' = CH_3; *(2e)*: R = C_6H_5, R' = CH_3; *(2f)*: R = CH_3, R' = C_6H_5; *(2g)*: R = R' = C_6H_5;
(3a): R = R' = OR''; *(3b)*: R = R' = CH_3; *(3c)*: R = C_6H_5, R' = CH_3; *(3d)*: R = CH_3, R' = C_6H_5; *(3e)*: R = R' = C_6H_5;
(5a): R = OR''; *(5b)*: R = CH_3; R'' = C_2H_5;
(7a): R = CH_3; *(7b)*: R = C_6H_5;
(8a): R = R' = CH_3; *(8b)*: R = CH_3, R' = C_6H_5.

Received, May 30th, 1963 [Z 523/351 IE]
German version: Angew. Chem. 75, 670 (1963).

[1] *E. Fahr*, Angew. Chem. *73*, 536 (1961).

[2] *R. Breslow, C. Yaroslavsky*, and *S. Yaroslavsky*, Chem. and Ind. *1961*, 1961.

[3] *K. Döppert*, Ph. D. Thesis, Universität Würzburg (now being completed). The synthesis of oxadiazolines *(2)* from the silver salts *(1)* is generally preferable to the interaction of diazofluorene and α,α'-dicarbonylazo compounds, as the latter are often difficult to obtain in a pure state. Furthermore, unequivocal synthesis of unsymmetrically substituted oxadiazolines [*e.g. (2e)* or *(2f)*)] via dicarbonylazo compounds is not possible.

[4] Concerning the nomenclature of *(3)*, cf. *R. Huisgen* and *A. Eckell*, Tetrahedron Letters *1960*, 5; *R. Huisgen, R. Grashey, P. Laur*, and *H. Leitermann*, Angew. Chem. *72*, 416 (1960).

[5] Crossing experiments served to exclude the possibility of intermolecular migration of the R·CO group.

[6] If the silver salt had an anionic oxadiazoline structure, bands due to an –N–C–O– grouping (part of a heterocycle) would be expected at 5.95 and 6.10 μ.

Explosion during the Synthesis of Dinitrosodimethyloxamide

By Dipl.-Chem. R. Preußmann

Laboratorium der Chirurgischen Universitätsklinik, Freiburg/Breisgau (Germany)

H. Reimlinger [1] described *N,N'*-dinitroso-*N,N'*-dimethyloxamide as a stable compound particularly suitable as a starting material for the preparation of diazomethane.

In one of several runs for preparing the substance, the carbon tetrachloride used as solvent while introducing the nitroso groups was distilled off not *in vacuo* but at normal pressure on a hot water bath in a hood. Towards the end of the distillation, an extremely violent explosion occurred. The distillation apparatus was completely shattered, and the hood was badly damaged. Two bystanders received cuts on the face and injuries to hearing as a result of the blast.

Accordingly, in dealing with dinitrosodimethyloxamide, maintenance of as low reaction temperatures as possible should be strictly observed. Reference has been made to the strongly carcinogenic properties of a number of nitrosoacylalkylamines [2].

Received, May 31st, 1963 [Z 518/347 IE]
German version: Angew. Chem. *75*, 642 (1963).

[1] *H. Reimlinger*, Chem. Ber. *94*, 2547 (1961).

[2] *H. Druckrey, R. Preußmann* et al., Naturwissenschaften *48*, 165 (1961); Nature (London) *195*, 1111 (1962).

The Subunits of the β-Galactosidase from Escherichia coli

By Dipl.-Chem. K. Weber, Dr. H. Sund, and Prof. Dr. K. Wallenfels

Chemisches Laboratorium der Universität Freiburg/Breisgau (Germany)

Crystalline β-galactosidase from *E. coli* ML 35 or ML 309 is split into subunits by guanidine-HCl, sodium dodecyl sulfate, urea, *p*-chloromercuribenzoate, or performic acid. Alkylation with iodoacetamide in 5 M guanidine-HCl brings about dissociation of the native enzyme molecule of molecular weight 518000 [1] into four subunits with particle weights of 147000 ($s^0_{20,w} = 3.65\times10^{-13}$ sec, $D^0_{20,w} = 2.50\times10^{-7}$ cm²/sec). Oxidation and subsequent treatment with sodium dodecyl sulfate gives rise to 12 subunits with particle weights of 43000 ($s^0_{20,w} = 2.09\times10^{-13}$ sec, $D^0_{20,w} = 4.93\times10^{-7}$ cm²/sec). Thus, it is clear that the enzyme molecule consists of at least 12 peptide chains, which, on the basis of sedimentation and diffusion measurements, are of equal size. Of these 12 chains, each group of three chains is bound together, thus making four larger subunits in all. While these larger subunits are certainly not joined together by covalent bonds in the native protein, it seems plausible to assume that disulfide bridges are involved in their formation from the smaller units.

The N-terminal group determinations that have been carried out so far [2] have led to the assumption that the equivalent weight of the mutually identical peptide chains in the β-galactosidase molecule must amount to approx. 135000 [3]. According to our results, the peptide chains are at least three times smaller than this. Thus, apart from those found hitherto, there must be at least eight further masked or substituted N-terminal groups present [4].

Received, June 4th, 1963 [Z 520/342 IE]
German version: Angew. Chem. *75*, 642 (1963).

[1] *H. Sund* and *K. Weber*, Biochem. Z. *337*, 24 (1963).

[2] *M. Cohn*, quoted in *J. Monod*, Angew. Chem. *71*, 685 (1959); *K. Wallenfels* and *A. Arens*, Biochem. Z. *333*, 395 (1960); *K. Wallenfels* and *C. Streffer*, Biochem. Z., in the press.

[3] *F. Jacob* and *J. Monod*, J. molec. Biol. *3*, 318 (1961); *F. Jacob* and *E. L. Wollman*: Sexuality and the Genetics of Bacteria. Academic Press, New York and London 1961, p. 253.

[4] A detailed report will be published in Biochem. Z.

Synthesis of Cyclopropyl Halides

By Dr. W. Kirmse [1] and B. Graf v. Wedel

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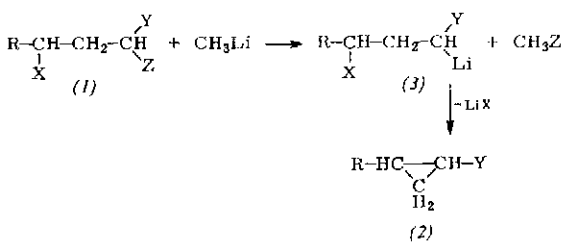
1,1,3-Trihalogenoalkanes *(1)*, which are obtainable by peroxide-catalysed addition of haloforms onto olefins [2], are converted by treatment with methyl-lithium in ether at −20 °C to 30 °C into cyclopropyl halides *(2)*. Starting from 1,1,3-tribromopropane *(1a)* we obtained 60–65 % yields of cyclopropyl bromide *(2a)*, which was identical with a specimen prepared by Hunsdiecker degradation of cyclopropanecarboxylic acid [3]. 1,1,3-Tribromobutane *(1b)* yielded *cis*- and *trans*-1-bromo-2-methyl-cyclopropane *(2b)*. In this cyclization, it is a 1-halogen that reappears on the ring, since 1,1-dibromo-3-chloropropane *(1c)* gave exclusively cyclopropyl bromide *(2a)*, while 1,3-dibromo-1-chloropropane *(1d)* gave cyclopropyl chloride *(2c)*. The reaction is initiated by a halogen-metal exchange, followed by 1,3-elimination of lithium halide.



(1a): R=H, X=Y=Z=Br; *(2a)*: R=H, Y=Br;
(1b): R=CH_3, X=Y=Z=Br; *(2b)*: R=CH_3, Y=Br;
(1c): R=H, X=Cl, Y=Z=Br; *(2c)*: R=H, Y=Cl;
(1d): R=H, X=Z=Br, Y=Cl; *(2d)*: R=H, Y=I;
(2e): R=CH_3, Y=I

Interaction of *(1a)*, *(1b)*, or *(1c)* with methyl-lithium in the presence of lithium iodide produces a mixture of cyclopropyl bromides *(2a)*, *(2b)* and cyclopropyl iodides *(2d)*, *(2e)*. Cyclopropyl iodide *(2d)* has recently been obtained by a multi-stage synthesis [4]; its physical properties, particularly its NMR spectrum, agree with those of our product. Since neither the trihalogenoalkanes *(1a)*, *(1b)*, *(1c)* nor the cyclopropyl bromides *(2a)*, *(2b)* react with lithium iodide under the conditions employed, it follows that the substitution must occur in the organometallic intermediate *(3)*. Our results indicate a two-stage mechanism for α-elimination in *gem*-dihalides.

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German version: Angew. Chem. *75*, 672 (1963).

[1] Present address: Chemisches Institut der Universität Marburg/Lahn (Germany)

[2] *M. S. Kharasch* et al., J. Amer. chem. Soc. *68*, 154 (1946).

[3] *J. D. Roberts* and *V. C. Chambers*, J. Amer. chem. Soc. *73*, 3176 (1951).

[4] *D. E. Applequist* and *D. F. O'Brien*, J. Amer. chem. Soc. *85*, 743 (1963).

Preparation and Properties of Tricyclo[3,3,2,$0^{4,6}$]deca-2,7,9-triene (Bullvalene)

By Dr. Gerhard Schröder

Union Carbide European Research Associates, Brussels (Belgium)

Doering and *Roth* [1] recently postulated and discussed tricyclo[3,3,2,$0^{4,6}$]deca-2,7,9-triene *(1)*, also known as bullvalene. This compound ought to show optimum possibilities for rapid and reversible valence isomerization. In the terminology of *Doering* and *Roth (1)* is the molecule with the ideal "fluxional structure".

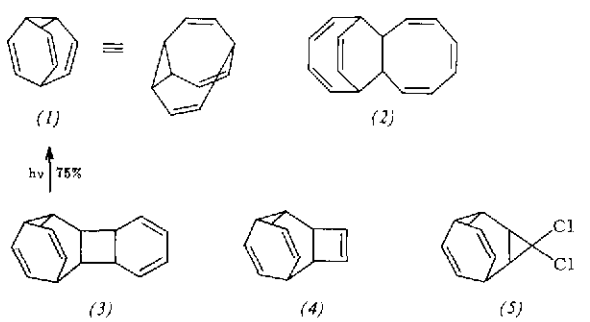
During research on the state of cyclooctatetraene in basic medium [2], two dimeric cyclooctatetraenes were isolated, which had been previously described by *W. O. Jones* [3]. These $C_{16}H_{16}$ hydrocarbons have m.p. 53 °C and 76 °C and structures *(2)* and *(3)*, respectively.

On hydrogenation, *(3)* absorbs 5 moles of hydrogen to give $C_{16}H_{26}$ [4], m.p. 52–54 °C. The ultraviolet spectrum of *(3)* exhibits a maximum at 282 mμ (ε = 2300) and a shoulder at 232 mμ (ε = 4600). Its Diels-Alder adducts with maleic anhydride, diethyl fumarate, and acetylenedicarboxylic ester absorb in the ultraviolet at λ = 232 mμ (shoulder, ε = 3000 to 6000). The acetylenedicarboxylic ester adduct decomposes at about 160 °C into dimethyl phthalate and $C_{12}H_{12}$ *(4)* [4], m.p. 22 °C. The ultraviolet spectrum of *(4)* also shows absorption at 232 mμ (shoulder, ε = 2300). Hydrogenation over palladium yields $C_{12}H_{20}$ [4].

Ultraviolet irradiation of *(3)* in ether affords $C_{10}H_{10}$ *(1)* [4] (75%; m.p. 96 °C) and benzene.

Hydrogenation of *(1)* over palladium gives $C_{10}H_{18}$ [4], m.p. 180 °C. Treatment of *(1)* with sodium in liquid ammonia at 75 °C and subsequent decomposition with methanol yields $C_{10}H_{12}$ [4], m.p. 45 °C, whose NMR-spectrum indicates a bicyclo[3,3,2]deca-3,7,9-triene structure. Compound *(1)* absorbs in the ultraviolet at 238 mμ (shoulder, ε = 1700). Its infrared spectrum has relatively few absorption bands. Oxidative degradation with ozone at −75 °C in methanol/ether, subsequent reduction with $NaBH_4$, and esterification with acetic anhydride [5] lead to $C_{12}H_{18}O_6$ [4], m.p. 58 °C, whose infrared and NMR-spectra are in accordance with a *cis*-1,2,3-tris(acetoxymethyl)cyclopropane structure. The NMR-spectra of *(1)*, *(3)*, *(4)*, and *(5)* are temperature-dependent [6]. At 100 °C the NMR-spectrum of *(1)* exhibits a most remarkable property, *viz.* only one sharp proton resonance signal at τ = 5,8. On cooling, this band broadens. At −25 °C, two bands are apparent, one centered at τ = 4.3 with a relative area of 6, the other centered at τ = 7.9 with a relative area of 4. Further cooling to −85 °C does not alter the spectrum. Compound *(1)* reacts with dichlorcarbene ($CHCl_3/(CH_3)_3COK$) to form a mono-adduct $C_{11}H_{10}Cl_2$ *(5)* [4], m.p. 101 °C.

(1) decomposes only above 400 °C to give naphthalene, via an as yet unidentified intermediate.



(1) *(2)* *(3)* *(4)* *(5)*

Compound *(1)* is bullvalene, *(3)*, *(4)*, and *(5)* are derivatives of homotropylidene [1].

Preliminary results indicate that *(2)* rearranges at 100 °C to form *(3)* with simultaneous formation of cyclooctatetraene.

Received, June 18th, 1963 [Z 537/367 IE]
German version: Angew. Chem. *75*, 722 (1963).

[1] *W. v. E. Doering* and *W. R. Roth*, Angew. Chem. *75*, 27 (1963); Angew. Chem. internat. Edit. *2*, 122 (1963); Tetrahedron *19*, 715 (1963).

[2] *G. Schröder*, Angew. Chem. *75*, 91 (1963); Angew. Chem. internat. Edit. *2*, 45 (1963).

[3] *W. O. Jones*, Chem. and Ind. *1955*, 16.

[4] All the new substances gave correct elemental analyses.

[5] Method: *A. J. Hubert*, J. chem. Soc. (London), in the press.

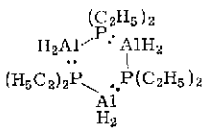
[6] The temperature-dependent NMR-spectra will be reported in a separate publication.

Diethylphosphidoaluminum Hydride and Lithium Diethylphosphidoaluminum Hydride

By Prof. Dr. G. Fritz and Dipl.-Chem. G. Trenczek

Institut für Anorganische und Analytische Chemie der Universität Gießen (Germany)

H_2AlCl reacts with $LiP(C_2H_5)_2$ *(1)* in ether to give the trimeric compound $[H_2Al-P(C_2H_5)_2]_3$ *(2)*, which is liquid at room temperature, crystallizes at 1–2 °C, and is not pyrophoric in air; molecular weight by cryoscopy in benzene: 350, calc. 356.



(2)

Compound *(2)* corresponds to $[Cl_2Al-P(C_2H_5)_2]_3$, which is obtained from $AlCl_3$ and one mole of $LiP(C_2H_5)_2$ [1]. It reacts with *(1)* according to:

$$[H_2Al-P(C_2H_5)_2]_3 + 3\ LiP(C_2H_5)_2 \rightarrow 3\ Li\ [AlH_2\{P(C_2H_5)_2\}_2] \quad (3)$$

Compound *(3)* is also obtained as follows:

$$H_2AlCl + 2\ LiP(C_2H_5)_2 \rightarrow LiCl + Li\ [AlH_2\{P(C_2H_5)_2\}_2]$$

It crystallises well, is colorless and inflammable in air, dissolves readily in THF but more sparingly in ether, and is very similar to $Li[Al\{P(C_2H_5)_2\}_4]$ [2].

Received, June 18th, 1963 [Z 526/358 IE]
German version: Angew. Chem. *75*, 723 (1963).

[1] *G. Fritz* and *G. Trenczek*, Z. anorg. allg. Chem. *313*, 236 (1961).

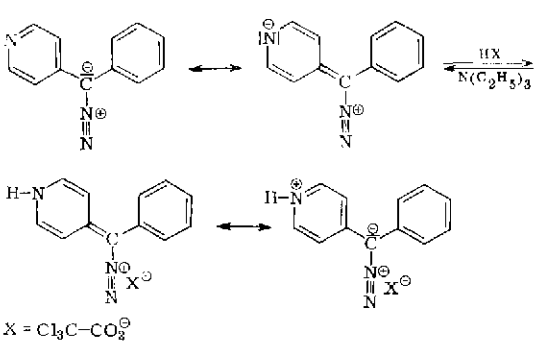
[2] *G. Fritz* and *G. Trenczek*, Angew. Chem. *74*, 942 (1962); Angew. Chem. internat. Edit. *1*, 663 (1962).

The Preparation of a Stable, Non-aromatic Diazonium Salt

By Dr. H. Reimlinger

Union Carbide European Research Associates S.A., Brussels (Belgium)

Aliphatic diazonium salts are hypothetical intermediates of deamination. The cyclization of α-pyridylphenyldiazomethane to a triazole derivative [1] suggests that a stable, non-aromatic diazonium salt might be obtained by adding a strong acid to γ-pyridylphenyldiazomethane.



The red solution of the diazo compound obtained by oxidation of α-hydrazono-4-benzylpyridine with silver oxide in pentane was evaporated to dryness *in vacuo* and the residue

recrystallized from petroleum ether (b.p. 40–60 °C), m.p. 64.5–66 °C, infrared absorption in KBr: N≡N 4.90 μ. The analytically pure diazo compound was dissolved in ether and trichloroacetic added; the diazonium salt precipitated as an orange-yellow compound, m.p. 97 °C (decomp.), infrared absorption in KBr: N≡N 4,85 μ; $=\overset{\oplus}{N}\!\!\diagup\!\!\diagdown$ broad band 3.5 to 4.4 μ). Elemental analysis gave values which confirmed the empirical formula $C_{14}H_{10}O_2N_3Cl_3$. The yellow aqueous solution of the salt is relatively stable.

When a solution of triethylamine in CCl_4 was added to a suspension of the diazonium salt in the same solvent, the product dissolved, and the diazo compound was regenerated. This reversibility is reminiscent of the system diazopyrazole/diazonium pyrazole [2].

Received, June 21st, 1963 [Z 527/353 IE]
German version: Angew. Chem. 75, 789 (1963).

[1] *J. H. Boyer, R. Borgers,* and *L. T. Wolford,* J. Amer. chem. Soc. *79,* 678 (1957); *J. D. Bower* and *G. R. Ramage,* J. chem. Soc. (London) *1957,* 4506; *J. H. Boyer* and *N. Goebel,* J. org. Chemistry *25,* 304 (1960).

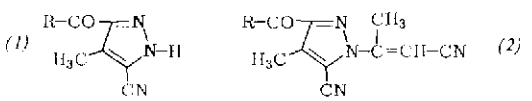
[2] *H. Reimlinger, A. v. Overstraeten,* and *H. G. Viehe,* Chem. Ber. *94,* 1036 (1961).

1:1- and 1:2-Adducts from Diazoketones and Cyanoallene

By Prof. Dr. W. Ried and H. Mengler [1]

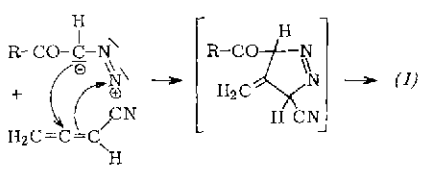
Institut für Organische Chemie der
Universiät Frankfurt/Main (Germany)

The substituted pyrazoles *(1)* and *(2)* have been prepared for the first time from diazoketones and cyanoallene [2].



(1) *(2)*

1,3-Dipolar addition of the diazoketone onto cyanoallene proceeds by way of an *exo*-methylenepyrazoline, and yields the energetically favorable aromatic pyrazole system.



The imino-hydrogen of the 1:1-adduct *(1)* may add onto a further molecule of cyanoallene, giving rise to the 1:2-adduct *(2)*. In some experiments, both *(1)* and *(2)* were isolated together. Aliphatic, aromatic, and heterocyclic diazoketones react analogously; bis-diazoketones produce bis-pyrazoles.

Examples:

	R	m.p. [°C]
1:1-Adducts *(1)*	H_3C-	122.5
	H_3C-CH_2-	106
	$H_3C-(CH_2)_{16}-$	92
	p-$H_3C-O-C_6H_4-$	147
1:2-Adducts *(2)*		
	H_3C-	86–87
	$H_3C-(CH_2)_{16}-$	45
	C_6H_5-	158,5
	p-$H_3C-O-C_6H_4-$	165
	β-$C_{10}H_7-$(β-Naphthyl)	147
	2,5-C_4H_2S-(Bispyrazolyl-)	241 [3]

Diazoalkanes, $R-CHN_2$, also react with cyanoallene to yield definite compounds, whose infrared spectra strongly suggest their analogy to *(1)* and *(2)*.

Cyanoallene + Diazomethane: Type *(1)*: m.p. 130 °C
Type *(2)*: m.p. 114 °C

Cyanoallene + Ethyl diazoacetate: Type *(1)*: m.p. 77–78 °C

Received, June 24th, 1963 [Z 531/355 IE]
German version: Angew. Chem. 75, 723 (1963).

[1] From the Ph.D. Thesis of *H. Mengler,* Universität Frankfurt/Main, 1963.

[2] Preparation according to *P. Kurtz, H. Gold,* and *H. Disselnkötter,* Liebigs Ann. Chem. *624,* 1 (1959).

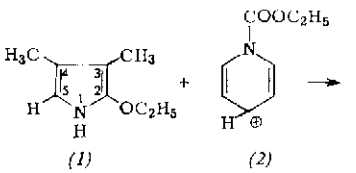
[3] Prepared from 2,5-bis(diazoacetyl)thiophene, m.p. 193 °C (decomp.), which was first obtained from thiophene-2,5-dicarboxylic acid; for the general method, cf. *B. Eistert,* in *W. Foerst:* Neuere Methoden der präparativen organischen Chemie. Verlag Chemie, Weinheim 1949, Vol. 1, p. 399.

Hydride Transfer in Heterocycles: The Conversion of Ethoxypyrrole Derivatives into Pyrrole Derivatives

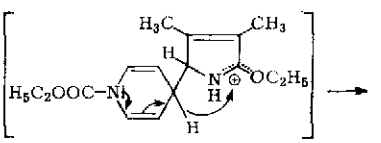
By Prof. Dr. H. Plieninger, Dipl.-Chem. U. Lerch, and Dipl.-Chem. J. Kurze

Chemisches Institut der Universität Heidelberg (Germany)

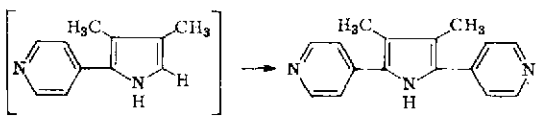
Treatment of 3,4-dimethyl-2-ethoxypyrrole *(1)* with ethyl chloroformate and pyridine gives a good yield of 3,4-dimethyl-2,5-dipyridylpyrrole *(5)*. The presumable course of reaction is indicated in formulae *(1)* through *(5)*. The last step entails a dehydrogenation that is not yet fully understood.



(1) *(2)*

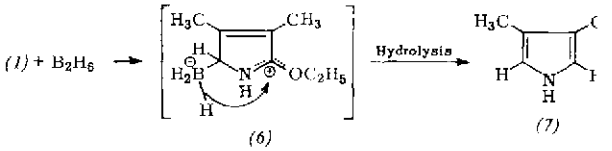


(3)



(4) *(5)*

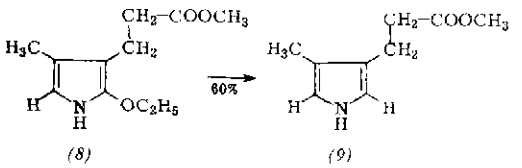
If diborane is used instead of *(2)*, the reaction with *(1)* gives over 70 % yield of 3,4-dimethylpyrrole *(7)* via a similar type of intermediate *(6)*.



(6) *(7)*

Since ethoxypyrroles can be produced from the readily available pyrrolones [1] using triethyloxonium fluoroborate, this new reaction forms a convenient mode of preparation of α,α'-unsubstituted pyrroles, which are important intermediates for the synthesis of porphyrins, chlorophylls, and bile pigments.

Thus, for example, methyl opsopyrrolecarboxylate *(9)* was obtained from the readily available ethoxypyrrole ester *(8)*.



(8) *(9)*

2-Ethoxyindole [1] can also be converted into indole with diborane.

Received, June 25th, 1963 [Z 530/349 IE]
German version: Angew. Chem. *75*, 724 (1963).

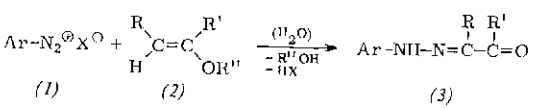
[1] *H. Plieninger, H. Bauer*, and *A. Katritzky*, Liebigs Ann. Chem. *654*, 165 (1962).

Coupling of Diazonium Salts with Enol Ethers

By Dr. M. Seefelder and Dr. H. Eilingsfeld

Farbenforschungslaboratorium der Badischen Anilin- & Soda-Fabrik AG, Ludwigshafen am Rhein (Germany)

Diazonium salts *(1)* couple with enol ethers *(2)* to give monoarylhydrazones of 1,2-dicarbonyl compounds *(3)*.



(1) *(2)* *(3)*

These monoarylhydrazones *(3)* can be converted with *p*-nitrophenylhydrazine into osazones.

p-Nitrophenyldiazonium chloride or fluoroborate couple with vinyl ethyl ether (R = R′ = H, R″ = C_2H_5) in water at 0–10 °C to give α-(*p*-nitrophenylhydrazono)acetaldehyde (m.p. 188–190 °C, decomp.); with *p*-nitrophenylhydrazine, this is converted into 1,2-di-(*p*-nitrophenylhydrazono)ethane (m.p. 310 °C, 311 °C [1]). Ethyl propenyl ether (R = CH_3, R′ = H, R″ = C_2H_5) and ethyl isopropenyl ether (R = H, R′ = CH_3, R″ = C_2H_5) couple to give isomeric *p*-nitrophenylhydrazonopropanones, which react further with *p*-nitrophenylhydrazine to give 2,3-di-(*p*-nitrophenylhydrazono)propane (m.p. 270 °C, 276–277 °C [2]).

Dihydrofuran reacts with *p*-nitrophenyldiazonium salts, yielding 2-(*p*-nitrophenylhydrazono)-4-hydroxybutyraldehyde (m.p. 118–120 °C, decomp.).

Received, June 28th, 1963 [Z 532/356 IE]
German version: Angew. Chem. *75*, 724 (1963).

[1] *A. Wohl* and *C. Neuberg*, Ber. dtsch. chem. Ges. *33*, 3107 (1900).

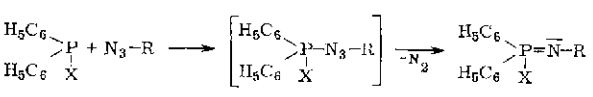
[2] *V. Wolf*, Chem. Ber. *86*, 843 (1953).

Stable Primary Adducts from the Staudinger Reaction

By Dr. H. Bock and Dipl.-Chem. W. Wiegräbe [1]

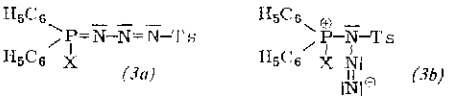
Institut für Anorganische Chemie der Universität München (Germany)

Studies on the reactivity of the P=N double bond led to the synthesis of numerous *N*-alkyl-, *N*-aryl-, and *N*-tosyl-phosphine imides *(2)* by the Staudinger reaction of phosphine derivatives with azides.



(1) *(2)*

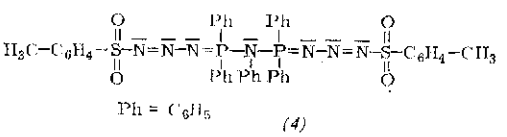
In the past, the adducts *(1)* initially formed have been secured in only a few cases [2]. We have isolated these adducts *(1)* in almost quantitative yields by reaction of substituted phosphines with tosyl azide. The adducts are lemon-yellow compounds *(3a)* or *(3b)* which decompose at 88 °C (X = C_6H_5),



(3a) *(3b)*

80 °C (X = NH–C_6H_5), and 72 °C (X = $N(C_3H_7)_2$). The linear structure of the (1-tosyltriazen-3-ylidene)phosphoranes *(3a)* is in accordance with infrared spectroscopical studies of the P=N stretching frequency [3]. Despite its strong resemblance to the spectra of comparable *N*-tosylphosphine imides [*(2)*, R = Ts], the customary coupling with the asymmetric SO_2 vibration is lacking in the spectrum of *(3a)* on account of the greater distance between the P=N and SO_2 groups [4]. No diazo band corresponding to *(3b)* appears in either the double or triple bond region.

N,N-Bis(diphenylphosphino)aniline H_5C_6–N[P(C_6H_5)$_2$]$_2$ reacts with two moles of tosyl azide to give the golden-yellow bis-[(1-tosyltriazen-3-ylidene)phosphoranyl]aniline *(4)* which decomposes at 103 °C and contains thirteen atoms of Group V and VI elements in a row.



Ph = C_6H_5

(4)

Received, July 1st, 1963 [Z 534/357 IE]
German version: Angew. Chem. *75*, 790 (1963).

[1] Communication No. 2 on Investigations of the Reactivity of the P=N Double Bond. Communication No. 1: *H. Bock* and *W. Wiegräbe*, Angew. Chem. *74*, 327 (1962); Angew. Chem. internat. Edit. *1*, 265 (1962).

[2] *H. Staudinger* and *J. Meyer*, Helv. chim. Acta *2*, 635 (1919); *E. Bergmann* and *H. A. Wolff*, Ber. dtsch. chem. Ges. *360*, 1176 (1930); *L. Horner* and *A. Gross*, Liebigs Ann. Chem. *591*, 117 (1955); *G. Wittig* and *K. Schwarzenbach*, Liebigs Ann. Chem. *650*, 1 (1961); *J. E. Leffler, U. Honsberg, Y. Tsuno*, and *J. Forsblad*, J. org. Chemistry *26*, 4810 (1961).

[3] *H. Bock* and *W. Wiegräbe*, unpublished data.

[4] *T. Moeller* and *A. Vandi*, J. org. Chemistry *27*, 3511 (1962).

Relationships between the Color and Constitution of Azophosphonic Acid Derivatives

By Dr. H. Bock, Dr. E. Baltin, and Dr. G. Rudolph [1]

Institut für Anorganische Chemie der Universität München (Germany)

Azodiphosphonic acid derivatives *(1)* are violet, phenylazophosphonic acid derivatives *(2)* are red.

(1) *(2)*

The unexpected color of these π-systems of limited size corresponds to a considerable bathochromatic shift of the low-intensity $n \rightarrow \pi^*$ transition of the azo group in the visible region (for comparison: azomethane 29000; the azodicarboxylic anion 25000; azobenzene 22750; the phenylazophosphonic anion 20700; the azodiphosphonic anion 18800 cm^{-1}). Variation of Y causes shifts in the long-wave absorption maximum in *(1)* and *(2)* with approximately constant differences in wave number ($\Delta\nu_{max}$ *(2)*–*(1)* = 2000 cm^{-1}) and hypsochromic in the order $C_6H_5 \backsim NR_2 > OR > O^{\ominus}$.

Table 1. Long-wave absorption maxima ν_{max} and oscillator strength f of *(1)* and *(2)* in dioxan or water (W).

Y	*(1)*		*(2)*	
	ν_{max} [cm^{-1}]	f [$\times 10^{-4}$]	ν_{max} [cm^{-1}]	f [$\times 10^{-4}$]
$-C_6H_5$	17700	3.5	19950	17
$-NR_2$	17700	2.3	19800	16
$-OR$	18000	2.6	20300	16
$-O^{\ominus}$	18850 (W)	1.8	20700	11

The intensities f decrease only slightly within each group of compounds, but differ markedly for *(1)* and *(2)*. For azobenzene f = 100 × 10^{-4}. Similar substituent effects on the band positions have been observed for unsymmetrically substituted azo compounds A–N=N–B, the long-wave absorption maxima of which lie, in all cases investigated, between those of A–N=N–A and B–N=N–B.

Table 2. Long-wave absorption maxima ν_{max} of unsymmetrically substituted azo compounds in dioxan.

A	B	A–N=N–A ν_{max} [cm^{-1}]	A–N=N–B ν_{max} [cm^{-1}]	B–N=N–B ν_{max} [cm^{-1}]
$PO-(C_6H_5)_2$	$-C_6H_5$	17700	19950	22750
$-PS(C_6H_5)_2$	$-C_6H_5$	18600	20300	22750
$-PO(C_6H_5)_2$	$-CO(C_6H_5)$	17800	19650	21350
$-CO(C_6H_5)$	$-COOR$	21350	23000	24700

These regularities have been confirmed with numerous azo compounds [2] and prompt us to assume that there are absorption increments which are characteristic for the substituents. The mechanism of the influence of substituents, *i.e.* increase in the n-term or decrease in the π^*-level, remains an open question. Investigations on solvatochromic effects and dipole moments of symmetrically substituted azo compounds [2] will be reported later.

Received, July 1st, 1963 [Z 535/368 IE]
German version: Angew. Chem. *75*, 789 (1963).

[1] Communication No. II on Inorganic Azo Comounds, Communication No. I: *H. Bock* and *G. Rudolph*, Chem. Ber. *94*, 1457 (1961). Dimethyl phenylazophosphonate was first described by *F. Suckfüll* and *H. Haubrich*, Angew. Chem. *70*, 238 (1958).

[2] *H. Bock, E. Baltin, J. Kroner*, and *G. Rudolph*, unpublished data.

Sequential Analysis of Peptides by Means of Mass Spectrometry and Gas Chromatography

By Prof. Dr. F. Weygand, Dr. A. Prox,
Dipl.-Chem. W. König, and Dipl.-Chem. H. H. Fessel

Organisch-Chemisches Institut der
Technischen Hochschule München (Germany)

The relatively high vapor pressure of the *N*-trifluoroacetyl (TFA) peptide esters [1] made it seem likely that it would be possible to obtain mass spectra not only of *N*-TFA-dipeptide esters [2] hut also of even higher peptides. Numerous *N*-TFA-tripeptide and *N*-TFA-tetrapeptide methyl esters were investigated [4] using a CH 4 Model mass-spectrometer [3]. An *N*-TFA-tetrapeptide for example, gave rise *inter alia* to the following characteristic ions:

$F_3CCO-NHCHRCO-NHCHR^1CO-NHCHR^2CO-NHCHR^3$,
$F_3CCO-NHCHRCO-NHCHR^1CO-NHCHR^2$,
$F_3CCO-NHCHRCO-NHCHR^1CO-NHCHR^2 + H$,
$F_3CCO-NHCHRCO-NHCHR^1$,
$F_3CCO-NHCHRCO-NHCHR^1 + H$,
$F_3CCO-NHCHR$,
$F_3CCO-NHCHR + H$,
$H_2NCHR^3COOCH_3 + H$.

From these an unequivocal sequential analysis of low oligopeptides is possible, even from mixtures.

On sequential analysis of long-chain peptides, esterification with methanol/HCl and *N*-trifluoracetylation following partial hydrolysis gave rise not only to dipeptides [5], but also to many tri- and tetrapeptides, which can be gas-chromatographed by application of temperature programming. A gas chromatogram of a partial hydrolysate of Leu-Leu-Val-Val gave peaks for the three possible dipeptides, both possible tripeptides, the unchanged tetrapeptide, and the two amino acids. The fractions can be collected and identified by mass spectrometry.

Received, July 2nd, 1963 [Z 533/360 IE]
German version: Angew. Chem. *75*, 724 (1963).

[1] *F. Weygand, R. Geiger*, and *W. Swodenk*, Angew. Chem. *68*, 307 (1956); *F. Weygand, G. Klipping*, and *D. Palm*, Chem. Ber. *93*, 2619 (1960).

[2] *E. Stenhagen*, Z. analyt. Chem. *181*, 462 (1961).

[3] Atlas Meß- und Analysentechnik, Bremen (Germany). The substances are introduced into the ion-source by means of a vapor lock (TO4-oven), cf. *G. Spiteller, C. Brunné, K. Heyns*, and *H. F. Grützmacher*, Z. Naturforsch. *17b*, 856 (1962).

[4] Spectra were also obtained from an *N*-TFA-pentapeptide methyl ester.

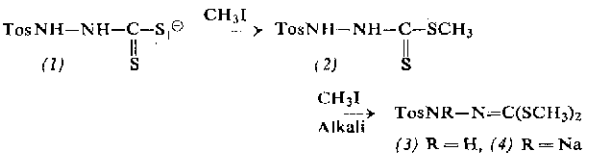
[5] *F. Weygand, A. Prox, E. C. Jorgensen, R. Axén*, and *P. Kirchner*, Z. Naturforsch. *18b*, 93 (1963), and earlier papers.

Di(methylthio)carbene (Carbon Monoxide Methyl Mercaptal) from Di(methylthio)diazomethane

By Doz. Dr. U. Schöllkopf and Dipl.-Chem. E. Wiskott

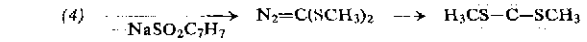
Organisch-Chemisches Institut der Universität Heidelberg (Germany)

Tosylhydrazide undergoes addition onto CS_2 in alkaline solution to yield *(1)*, which may be alkylated successively with methyl iodide to form the (isolated) monoester *(2)* and thence the tosylhydrazone of *S,S*-dimethyldithiocarbonic acid *(3)*, m.p. 151 °C.

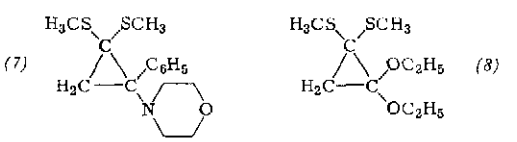


(3) R = H, *(4)* R = Na

On stirring with sodium hydride in aprotic solvents, *(3)* yields *(4)*, which decomposes at approx. 120 °C into sodium toluene-*p*-sulfinate and *(5)*. The latter splits off nitrogen and apparently yields *(6)*.



On decomposing *(4)* in 1-morpholino-1-phenylethylene or ketene diethylacetal, the intermediate *(6)* can be trapped in the form of the cyclopropane adducts *(7)* (32%, m.p. 60 °C) or *(8)* (30%, b.p. 114 °C/12 mm).



In addition, tetra(methylthio)ethylene [1] and trimethyl orthothioformate are also formed. The carbene does not undergo addition onto cyclohexene (in diglyme); apparently its electrophilic nature is reduced by the two sulfur atoms (owing to their unshared doublets) to such an extent that it adds only to particularly electron-rich double bonds.

Received, July 5th, 1963 [Z 538/366 IE]
German version: Angew. Chem. *75*, 725 (1963).

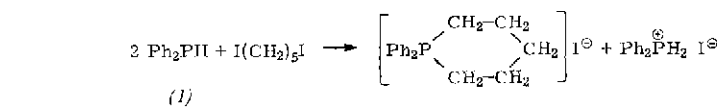
[1] Tetra(methylthio)ethylene is also obtained when trimethyl orthothioformate is treated with potassamide in ammonia. Di-(methylthio)carbene is considered to be an intermediate in this reaction; cf. *J. Hine, R. P. Bayer*, and *G. Hammer*, J. Amer. chem. Soc. *84*, 1751 (1962).

Cyclic Phosphonium Salts

By Prof. Dr. S. O. Grim and Dr. R. Schaaff [*]

Department of Chemistry, University of Maryland, College Park, Maryland (U.S.A.)

We have found that on refluxing diphenylphosphine *(1)* and 1,5-diiodopentane in acetonitrile in a nitrogen atmosphere for 12–16 hours cyclopentamethylenediphenylphosphonium iodide *(2)*, m.p. 278–279 °C, is produced in 45 % yield. The colorless crystalline compound shows no P-H stretching peak in the infrared. The reaction presumably proceeds via diphenyl-5-iodopentylphosphine by intramolecular quaternization

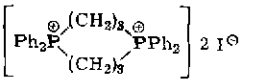


(1) *(2)*

Ph = C_6H_5

The cyclic salt *(2)* is reduced by $LiAlH_4$ in tetrahydrofuran to give cyclopentamethylenephenylphosphine and benzene, which was identified by gas chromatography.

Reaction of 1,3-diiodopropane with *(1)* furnished a smaller yield of *(3)*, m.p. 204–205, whose molecular weight in nitrobenzene indicates a cyclic, dimeric structure:



A similar compound results from tertiary 2-bromoethylphosphines [1]. No evidence was found for the formation of a 4-membered heterocyclic ring.

Received, May 21st, 1963 [Z 515/365 IE]
German version: Angew. Chem. 75, 669 (1963).

[*] The authors thank the National Science Foundation for financial support.

[1] *C. H. S. Hitchcock* and *F. G. Mann*, J. chem. Soc. (London) *1958*, 2081.

CONFERENCE REPORTS

Swiss Chemical Society

A symposium on the topic "Application of Physical Methods to Chemical Problems" was held at Basel on February 23rd, 1963.

From the agenda:

Applications of Circular Dichroism in Organic Chemistry

G. Ourisson, Strasbourg (France)

Correlations exist between rotatory power and circular dichroism [1]. Many chromophores cause circular dichroism in a suitable asymmetric environment. This was demonstrated by means of examples from unsaturated nitro compounds, homocyclic dienes, unsaturated acids, but principally on saturated and unsaturated ketones.

The method [2] can be applied to problems of structural analysis (*e.g.* proof of the presence of a keto group) and stereochemical questions. The octant rule developed for the interpretation of results from rotatory dispersion measurements can be applied directly to circular dichroism. The conformation of ring A of triterpenes, which exists as a strongly deformed chair structure, has been clarified by means of circular dichroism (as well as by other physical methods).

Light Absorption and Changes in Molecular Properties

H. Labhart, Basel (Switzerland)

On absorbing light energy, molecules remain for at least 10^{-8} sec in the exited state, which should therefore be regarded as a real intermediate.

Energies, charge distribution, and dipole moments were calculated by the SCF–MO (self-consistent field - molecular orbital) method proposed by *Pariser* and *Parr*, using a computer (IBM 7090, IBM 1620). Both, the dipole moment in the exited state and the polarization of the transitions, were determined experimentally from the band shift and dichroism in a strong electric field (10^5 volt/cm) [3]. With the test samples (nitrobenzene and benzaldehyde), there was satisfactory agreement between the calculated and experimental values. There is a correlation between the chemical reactivities and charge densities (photoreactivities).

The experimental method mentioned offers a useful supplement to existing methods for the interpretation of electronic spectra of organic molecules.

Observation of the Three-dimensional Structure of Large Molecules with the Electron Microscope

M. Thürkauf, Basel (Switzerland)

An image was produced of the three-dimensional structure of large fibrous molecules which assume a coiled configuration in solution. For the preparation of the samples, a high vacuum set-up was developed, in which the solution is sprayed onto the carrier foil of an electron microscope, freeze-dried at −170 °C, and shadowed with metal vapor. The vacuum was not interrupted between freeze-drying and shadowing. Freeze-drying prevents deformation of the three-dimensional coil by the surface tension of the solvent during the process of evaporation. In spite of a vapor source temperature of about 1400 °C, it was possible to maintain a radiation temperature of −170 °C at the site of the sample during vapor shadowing. This temperature was measured by a black thermocouple, that was strongly insulated against thermal conductivity. The low temperature was confirmed on water vapor samples, where the shadows of frozen fog droplets were visible down to diameters of about 100 Å.

At present, attempts are being made to produce images of the shape of deoxyribonucleic acid molecules in buffered solution. The samples are freeze-dried and shadowed with platinum-carbon vapor. Electron microscope images with clearly visible three-dimensionally coiled fibers of the expected diameter encased in Pt C were obtained. It is probable that these do not represent single DNA molecules but gel-like aggregates of a number of molecules, within which the single three-dimensionally coiled fibers can be made visible.

[1] Work of the Basel school: *W. Kuhn*; work of the UCLAF research group; *L. Velluz* and *M. Legrand*, Angew. Chem. *73*, 603 (1961).

[2] Measurements with a registering instrument made by Messrs. Jouan.

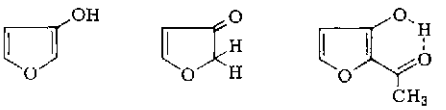
[3] *H. Labhart*, Chimia *15*, 20 (1961).

Solution of Organic Chemical Problems by Nuclear Magnetic Resonance Spectroscopy

W. von Philipsborn, Zurich (Switzerland)

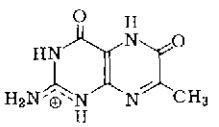
Applications of nuclear magnetic resonance spectroscopy to solve problems of tautomery, to clarify a reaction mechanism with the aid of deuterium substitution, and the significance of proton spin-spin coupling for the analysis of complicated spectra were discussed.

Derivatives of β-hydroxyfuran *(1)* occur to over 99 % in the Δ^2-furenid-4-one form *(2)*. The single exception known up to now is 2-acetyl-3-hydroxyfuran (isomaltol), which exists exclusively in the enol form *(3)*, being stabilized by hydrogen bonding, as can be proved by its nuclear magnetic resonance spectrum.



(1) *(2)* *(3)*

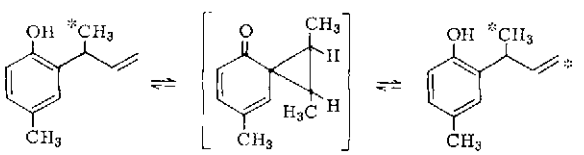
It was proved that 7-methylxanthopterine has the monoprotonized lactam structure *(4)* in CF_3COOH. The spectrum shows four separated absorptions of five (1×2 and 3×1) protons bound to nitrogen.



(4)

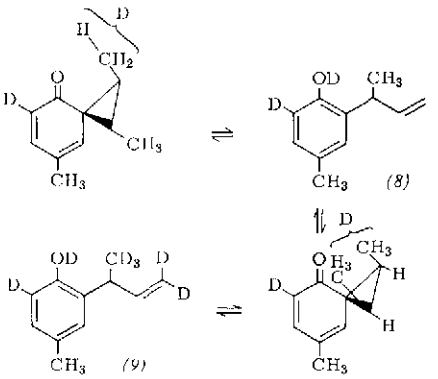
The enone structure =CH CO–COOH was deduced for the C_3-side chain of the red butterfly dyestuff erythropterine instead of the –CH=C(OH)–COOH enol structure previously postulated. Thus the ultraviolet spectrum of the dye, which is unusual for a pteridine acquires a rational explanation.

The thermal rearrangement of 2-(α-[^{14}C]-methyl-allyl)-4-methylphenol *(5)*, known as the anomalous Claisen rearrangement, to the doubly labelled phenol *(7)* proceeds via the spirodienone *(6)* postulated by *Marvell*.



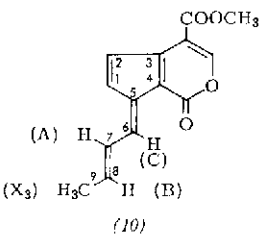
(5) *(6)* *(7)*

The rearrangement of the deuterated phenol *(8)* in D_2O leads to a phenol *(9)* whose proton and deuterium resonance spectra show that deuterium is attached only in the CH_3- and $=CH_2$-group of the side chain in agreement with the proposed mechanism. Quantitative evaluation by electronic integration gave a ratio of 1 : 2 between the degrees of deuteration in the CH_3- and $=CH_2$ groups. This result proves the intramolecular path of the rearrangement, since a prototropy could apparently be possible only from the methyl group in the *cis*-position to the carbonyl group.



(8) *(9)*

The configuration of the side chain of fulvoplumierin *(10)* can be determined unequivocally from its proton resonance spectrum by use of the spin-spin coupling method. Coupling of the methyl group in the $ABCX_3$ system under discussion simplifies this to an ABC-(ABX)-system, from which the *trans*-configuration of the 7,8-double bond follows on the basis of $J_{AB} = 13.9 \pm 0.7$ cps. The configuration of the 5,6-double bond can also be deduced *inter alia* from the resonance position [7.87 ppm of TMS (total magnetic susceptibility)] of the proton at the C-6 position.



(10)

[VB 695/85 IE]

German version: Angew. Chem. *75*, 477 (1963).

Meeting of French and German Chemists

Tübingen (Germany), April 25–27th, 1963

From the agenda:

Enrichment of Binary Gas Mixtures by Removal of the Adsorbates

C. Eyraud, Lyons (France)

When applied to adsorbed phases, static investigation methods do not render it possible to predict all the effects that are caused by dynamic processes, *e.g.* the permeability to vapors of micro-porous solids or enrichment effects produced by removal of the adsorbate.

The permeability minima of a porous body in relation to a condensable vapor at a pressure corresponding to a monomolecular coating are explained as being due to "diminution of the pore diameter" or "solidification" of the adsorbate.

The lecturer dealt mainly with the influence of the removal of the adsorbates on the separation effect of gas diffusion membranes. Experiments with hydrocarbon isomers show the importance of molecular structure for the surface mobility of the molecules. The enrichment observed in the mixture H_2O/DHO is attributed to the different types of interaction between molecule and solid, *i.e.* to a specific differential mobility of H_2O and DHO. If there is any mass effect, it will probably be of the next lower order of magnitude in this case.

Production of Fine-Grain Metal Carbides

R. A. Paris and *E. Clar*, Lyons (France)

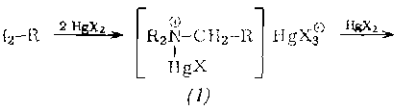
Metal carbides are usually prepared at high temperatures by fusion in an annular kiln or by solid-state reactions. These techniques, as well as that of electrolytic fusion, lead to the

production of more or less pure, but always crystalline, carbides. Conversions into carbides of finely-divided metals or metal oxides using carbonaceous gases, such as carbon monoxide or hydrocarbons, have been attempted in only a few cases. The authors studied carbide formation from reactive oxides and CH_4 or H_2/CH_4 mixtures, since in this way finely-divided carbides can be produced at lower temperatures. Transition metal carbides of groups IVa, Va, and VIa of the periodic table can also be prepared – particularly those of Mo, W, V, Cr, Ti, Ta, and Nb. An H_2/CH_4 mixture at 700–1000 °C will completely convert pyrolysis residues of less stable organic complexes or ammonium salts into the carbides. The carbides were identified by analysis and by their X-ray diagrams. The latter display long lines in most cases, indicating particle sizes of less than one micron. The specific surface area of these powders is of the order of several m^2/g.

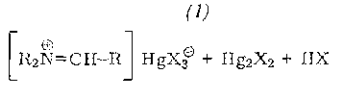
Mercuration of Tertiary Amines and Enamines

K. Brodersen, Aachen, and *G. Opitz*, Tübingen (Germany)

Mercuration of triethyl-, tripropyl-, and tributylamine with $HgCl_2$ or $HgBr_2$ in ether leads to the ammonium salts *(1)*.



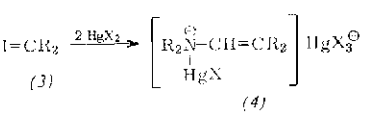
(1)



(2)

In polar solvents such as acetonitrile or nitromethane, dehydrogenation to the immonium salts *(2)* then occurs. These exhibit characteristic C=N bands in the 6 μ region of the infrared spectrum. Hydrolysis yields the corresponding aldehydes.

Simple tertiary vinylamines *(3)* react with $HgCl_2$ or $HgBr_2$ in ether to yield α,β-unsaturated ammonium salts *(4)* by *N*-mercuration.



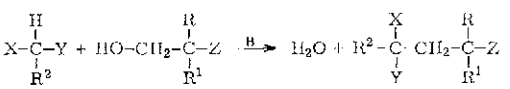
(3) *(4)*

The conversion of the vinylamines into *(4)* is accompanied by a bathochromic shift of the double bond band in the infrared spectrum in contrast to the hypsochromic shift on immonium salt formation.

The Reaction of ß-Ketols and Molecules with a Reactive Hydrogen Atom

J. Dreux and *M. Longeray*, Lyons (France)

Condensations of the type



were studied in order to elucidate the reaction mechanism. Experiments showed that condensation occurs when the hydroxymethyl compound can be dehydrated (R=H), or when there is a possibility of transhydroxymethylation, forming a new compound that can be dehydrated.

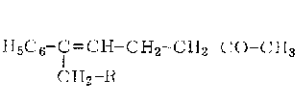
The reaction does not take place when the hydroxymethyl group is attached to a completely substituted carbon atom, or when the reactive hydrogen atom of the other reactant is attached to a tertiary carbon atom. This fact precludes an S_N2 mechanism.

Properties of Secondary γ,δ-Unsaturated Ketones and Alcohols

J. Colonge, Lyons (France)

γ,δ-Unsaturated ketones of type *(5)* are converted into dihydrobiphenyl derivatives on treatment with polyphosphoric acid. On heating with sulfur these hydrocarbons form substituted biphenyls *(6)*.

A mechanism is proposed for this cyclization: it recalls the reversible protonization which precedes cyclization to a tertiary alcohol with subsequent elimination of water.



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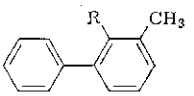
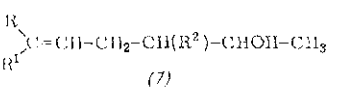


(6)

Secondary γ,δ-unsaturated alcohols of type *(7)* are converted into saturated ketones *(8)* by polyphosphoric acid. It is possible that this isomerization proceeds via a polyhydroxytetrahydropyran, for the action of polyphosphoric acid on 2,2,6-trimethyltetrahydropyran leads to 2-methylheptan-6-one.



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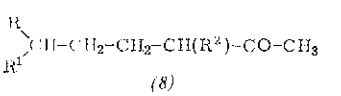


(8)

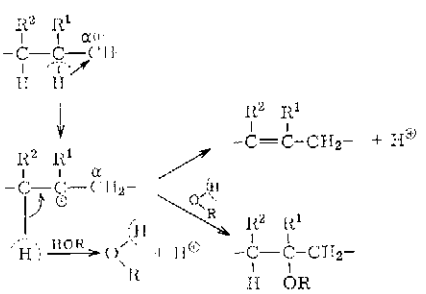
This isomerization resembles the rearrangement of 2,6,6-trimethyltetrahydropyran-2-carboxylic acid (cinenic acid) to 2,2-dimethylheptan-6-one-1-carboxylic acid (geronic acid) [1].

Elimination Reactions

W. Hückel, Tübingen (Germany)

The most important types of elimination reaction involve either monomolecular or pseudo-monomolecular elimination of an anion with subsequent elimination of a proton (E 1^-) or bimolecular elimination (E 2^1), where the attack of the reagent is directed at a proton.

The scheme formulated by *Hughes* in 1935 for E 1 elimination requires supplementation, because anomalous eliminations often occur which proceed with intramolecular anionic migration of hydrogen and a double bond shift, accompanied by anomalous substitution which leads to tertiary alcohols or derivatives.



Thus, (+)-neomenthylamine and nitrous acid gives – in addition to 20 % Δ^2-menthene – a Δ^3-menthene, 2/3 of which are racemized; this can be explained by intermediate formation of a tertiary carbonium ion at C-4, which is also indicated by the formation of menthan-4-ol as well as a little (–)-menthol. Further examples are afforded by the alcoholysis of the toluenesulfonates of α-decalols, which in addition to the normal elimination product, *viz.* $\Delta^{1,9}$-octalin,

[1] *H. Rupe* and *C. Liechtenhan*, Ber. dtsch. chem. Ges. *41*, 1278 (1908).

even in the absence of acid also gives varying quantities of $\Delta^{9,10}$-octalin, and, once again, also involves anomalous substitution which results in t-9-decalyl ethers in addition to the normal s-1-decalyl ethers.

The hydride displacement must always lead to Saytzeff elimination; its preponderance in many cases is thus explicable. Geometrically isomeric alcohols and amines behave differently on solvolysis of their toluenesulfonates. *cis*-Isomers give predominantly Δ^1-Saytzeff hydrocarbon and much anomalous substitution, whilst *trans*-isomers always give more Δ^2-Hofmann hydrocarbon than the *cis*-isomers, and often, when the neighboring group in the cyclohexane ring is a higher alkyl group, give Δ^1- and Δ^2-isomers in equal quantity. This rule is not valid for five-membered rings.

The 4-centre principle, which requires coplanarity for the elimination process, does not hold for E 1 elimination; the analogy to E 2 elimination required by *Barton* is not confirmed by the reaction products. Repeatedly there is direct opposition; on alcoholysis, menthyl toluenesulfonate gives 68 % of a 1/4 racemised Δ^3-menthene; reaction with alkoxide yields almost pure Δ^2-menthene.

$1^t,9^c,10^c$-α-Decalol (m.p. 62 °C) – as its toluene sulfonate – gives 61 % $\Delta^{1,2}$-octalin by E 1 and 100% by E 2, whereas its isomer $1^c,9^c,10^t$-α-decalol (m.p. = 49 °C) gives 1 % by E 1, and at least 67 % by E 2.

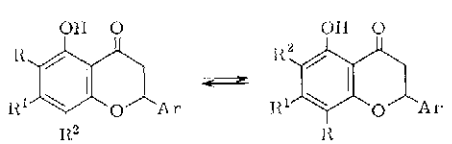
The question still remains to what extent the residual 23 % $\Delta^{1,9}$-octalin (+ some $\Delta^{9,10}$-octalin) result from a competitive E 1 reaction. In general, with rapidly solvolysed toluenesulfonates, it is often difficult to decide the ratio in which E 1 and E 2 eliminations occur side by side.

Owing to its relatively rigid structure, is it impossible for $1^t,9^c,10^c$-α-decalol to fulfil the demands of the 4-centre principle, which requires coplanarity in the transition state of the elimination reaction, whether it be E 1 or E 2, and whether it be in the direction of the $\Delta^{1,2}$- or $\Delta^{1,9}$-product.

Rearrangements in the 5,6- and 5,8-Dihydroxyflavanone Series

J. Chopin, Lyons (France)

Derivatives of both 5,6- and 5,8-dihydroxyflavan-4-one were synthetized in order to examine their ability to undergo the following rearrangement:



(9) *(10)*

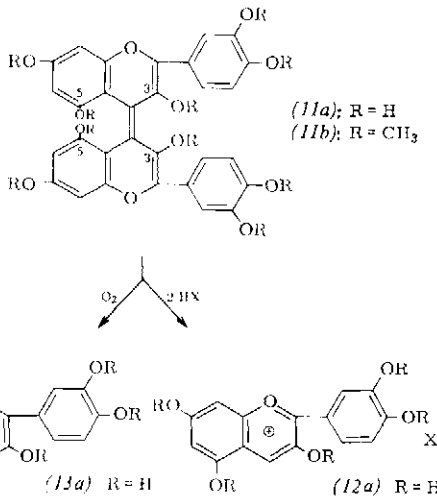
On treatment of 5-hydroxy-8-methoxyflavanone *(9)*, where $R = R^1 = H$, $R^2 = OCH_3$, $Ar = C_6H_5$ with alkali or heat but not, however, with acid, it is completely isomerized to 5-hydroxy-6-methoxyflavanone; however, the 5,8- and 5,6-dihydroxyflavanones resist all attempts at isomerization.

This unusual resistance to cleavage of the oxygen heterocycle disappears on introduction of a methoxyl group into the 4'-position of the 2-phenyl residue ($Ar = p\text{-}H_3CO\ C_6H_4$). 5,8-Dihydroxy-4'-methoxyflavanone isomerizes completely on treatment with alkali to the 5,6-dihydroxy-4'-methoxyflavanone.

Synthesis and Properties of Quercetylenes

E. Bayer, Tübingen (Germany)

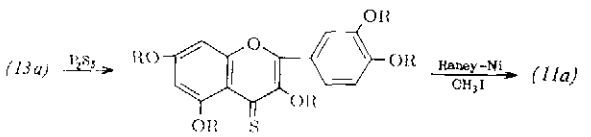
Malkin and *Nierenstein* claim to have obtained quercetylene *(11a)* from quercetin by reductive dimerization. The substance is significant as an intermediate in anthocyan metabolism since, theoretically, it is at the oxidation level of anthocyan *(12a)* and may be converted by oxidation into flavones *(13a)*. Anomalous behaviour of the double bond would be expected owing to the steric hindrance by the substituents in the *ortho*- and *peri*-positions.



(11a): R = H
(11b): R = CH_3

(13a) R = H *(12a)* R = H

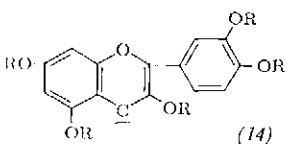
Since several authors also claim to have isolated quercetylene from plants, an attempt was made to synthetize the substance. The elemental analysis of the product obtained by the method of *Malkin* and *Nierenstein* is in accord with a quercetylene hydrochloride. Chromatographic investigations show, however, that the product is not uniform and contains cyanidin chloride and phlobaphene, but not a trace of a substance resembling quercetylene. For this reason, deca-*o*-methylquercetylene was synthetized as follows:



(13a) *(11a)*

It was established that the earlier compounds claimed as quercetylene cannot be regarded as such.

Quercetylene can be converted into quercetin *(13a)* by atmospheric oxygen at 100 °C. Molecular-weight determinations at elevated temperatures indicate that *(11b)* is dissociated. One of the limiting canonical structures for the dissociation product would be the carbene *(14)*. Compound *(11a)* is not piezochromic, but biflavylenes which have no substituents in the 3- and 5-positions are piezochromic; however, they do not substantially dissociate at elevated temperature. Instead, these substances show piezomagnetism, *i.e.* the compounds sometimes become paramagnetic under pressure. The paramagnetism disappears again on removing the pressure. This appears to be the first evidence of piezomagnetism in organic substances.



(14)

Steric and Electronic Effects in Nucleophilic Aromatic Substitution

H. Suhr, Tübingen (Germany)

The rate of reaction of uncharged Lewis bases with uncharged fluorine compounds, *e.g.*

$$R{-}C_6H_4F + C_5H_{11}N \rightarrow R{-}C_6H_4{-}NC_5H_{10} + HF$$

was investigated. On alteration of the activating substituent R, differences in rate of six powers of ten were found. The

influence of the substituent obeys the Hammet relationship, with a ρ-value of 7.2. In addition, *p*-nitrofluorobenzene was treated with numerous Lewis bases. It was shown that here steric effects are in general much more strongly marked, and hence largely determine the occurrence of reaction. Within a group of sterically equivalent compounds, electronic effects once again determine the rate of reaction.

Electrochemical Investigations of the Reducing Properties of Liquid Amalgams

J. C. Merlin and *M. Breant*, Lyons (France)

When using liquid amalgams for the reduction of organic compounds or inorganic ions, it is difficult to predict their reducing power because the reaction can proceed irreversibly as soon as equilibrium conditions are disturbed. We have plotted current intensity *vs.* potential curves by both polarography and linear chrono-amperometry. Relatively concentrated amalgams of Bi, Pb, Sn, Cd, Ga, In, and Th were investigated, but not those of alkali and alkaline-earth metals which reduce water.

If the ions formed as a result of oxidation of the amalgamated metal are precipitated or complexed, the half-wave potential is displaced to a less positive value corresponding to an increase in the reducing capacity of the amalgam. Intensity *vs.* potential curves were plotted under the following conditions:

(a) at a constant ionic strength of 1.0; (b) at different pH values so that the formation of hydroxylated ions and hydroxides could be controlled; buffer solutions which did not form complexes with the metal ions had to be employed; (c) in the presence of complexing agents, so that the effect of complex formation on the half-wave potential could be investigated.

It was possible to classify the reducing capacities of the various amalgams and to predict the course of some reactions. These predictions were tested and confirmed by the reduction of Eu^{2+} and *o*-dinitrobenzene.

Hydrolysis of Diborane on Silica Gel and Alumina Gel

M. V. Mathieu, Lyons (France)

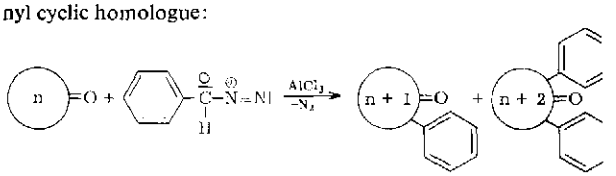
The hydrolysis of diborane by hydrated solid particles permits both differentiation between molecular water of constitution and "free" hydroxyl groups and determination of the number of hydroxyl groups per unit area. It is assumed that two molecules of water of constitution react with one molecule of diborane to form $-OBH_2-$ groups, while "free" hydroxyl groups react with diborane to form $-OB_2H_5$ groups. The structure of hydrolysed diborane was studied by infrared spectroscopy to test this working hypothesis. If the surface of the silica gel contains hydroxyl groups only, then the formation of $-OB_2H_5$ by reaction with the hydrogen atoms B–H···B of diborane is feasible. Formation of –B–O–B– chains and $-BH_2$ and $-BH_3$ groups, which display typical absorption bands, occurs. Molecular water seems to cause cleavage of diborane with formation of two $-OBH_2$ groups. The alteration in the symmetry of the molecule is responsible for the observed variation in the intensity of the symmetrical absorption band.

Treatment of alumina gel with diborane at 20–150 °C results in the formation of $-OBH_2$ groups. Infrared spectra confirm this hypothesis. The absorption band of diborane is much broader and displaced towards lower frequencies than in the case of silica gel. The bonds between the boron atoms and the surface must be stronger. The chemical reactions and the mass spectrum of alumina gels, which were treated at higher temperatures, indicate incipient polymerisation. In addition to the bands already described, the infrared spectra display a very broad band at lower frequencies. This must be due to polyborane chains, whose boron atoms are bound to the surface oxygen by coordinate bonds.

Catalytic Ring Expansion of Cycloalkanones and Steroid Ketones with Phenyldiazomethane

R. Heischkeil, Tübingen (Germany)

The idea of producing next higher homologues of rings using phenyldiazomethane follows as a logical consequence of the catalytic ring expansions with diazomethane discovered by our research group at Tübingen. Extension of the reaction to phenyldiazomethane attains satisfactory success only when petroleum ether is used as solvent instead of ether. Undesirable side reactions which occur in ether are largely suppressed in petroleum ether; simultaneously, the yields of homologous phenylcycloalkanones obtained increase considerably. In addition, it proves possible to introduce a second benzylidene group to give the next higher α,ω-diphenyl cyclic homologue:



The products are separated by fractional distillation *in vacuo* and purified by several recrystallizations.

This reaction for producing cyclic homologues becomes somewhat more complicated when applied to α,β-unsaturated ketones of the steroid series (Δ^4-cholesten-3-one, testosterone acetate, progesterone), both from the theoretical and practical points of view. The reaction products are separated on a column of inactivated alumina. Analysis of the fractions by thin-layer chromatography indicated a few isomeric reaction products which appear to be both conjugated and unconjugated A-homophenyl steroid ketones, judging from their ultraviolet and infrared spectra. [VB 699/87 IE]

German version: Angew. Chem. 75, 725 (1963)

Meeting of the German Pharmacological Society

April 28th to May 1st, 1963 in Mainz, Germany

From the agenda:

Pharmacological and Biochemical Characteristics of 6-Aminonicotinamide

A. Brunnemann and *H. Coper*, Berlin-Dahlem (Germany)

In rats and other mammals, 6-aminonicotinamide produces toxic effects which become especially apparent in progressive paralysis of the hind extremities. There is also a marked drop in body temperature accompanied by blood-stained diarrhoea; after considerable loss in weight, the animals die within a few days. Following intraperitoneal application of 25 mg/kg of 6-aminonicotinamide, 50 % of the animals die within 5 days. Neither artificial feeding nor increase in external temperature clearly influences the survival period. On the other hand, the prolongation of barbiturate narcosis by 6-aminonicotinamide is temperature-dependent.

The toxic action is caused by incorporation of the antimetabolite into the NAD molecule. To test this hypothesis, the 6-aminonicotinamide analogue of NAD (6-ANAD) was synthetized with the help of an NAD-nucleosidase from brain microsomes and its identity checked both by spectro-

photometry and by determination of the content of ribose, phosphate, and the 6-aminonicotinamide base.

In contrast to NAD, 6-ANAD is practically unaffected by enzymatic hydrolysis. The rate of reaction of malic acid dehydrogenase from pig heart and alcohol dehydrogenase from yeast and horse liver with 6-ANAD as cofactor is immeasurably small compared with that measured with NAD. The analogue acts as an inhibitor of various enzymic reactions. With a 1:1 mixture of NAD and 6-ANAD, the activities of malic dehydrogenase from pig heart and of phosphoglyceraldehyde dehydrogenase from rabbit muscle are significantly reduced. The phosphorylation of NAD by sheep heart mitochondria is almost completely inhibited when 10 % NAD is replaced by the analogue.

Acceleration of Drug Metabolism by Enzyme Induction

H. Remmer, M. Siegert, and *H.-J. Merker*, Berlin (Germany)

The accelerated oxidation of drugs *in vivo* and *in vitro* only 24–48 hr after a single administration of various lipid-soluble drugs is caused by non-specific induction of the microsomal enzymes which metabolize many drugs. Two microsomal fractions were obtained by ultracentrifugation in 45 % sucrose solution of equal amounts of liver from rabbits which had received a total of 300–400 mg/kg of phenobarbitone (50 mg/kg intraperitoneally every second day) and from untreated controls. The two fractions correspond to the smooth and rough membranes (*Palade*) of the endoplasmic reticulum. Only the rough fractions have ribosomes and serve for protein synthesis. Following administration of phenobarbitone, the protein and lipid content increased 2 to 3 times in the smooth fraction exclusively; the RNA content, however, was raised only by 70 %; in the rough fraction, no significant increase could be detected. Neither the liver weight nor the nitrogen contents of the nuclei, mitochondria, and cytoplasm were altered by treatment. With the increase in the smooth membranes, the activity of the enzymes metabolizing drugs rises by 2 to 6 times. TPNH-oxidase, cytochrome reductase, various drug oxidases, nitro reductase, and procaine esterase were investigated. On the other hand, the activities of glucose-6-phosphatase, TPN-nucleosidase, and ATPase remained unchanged.

The threefold rise of the microsomal cytochrome-b_5 content (direct spectrophotometric measurement) and the increase in the maximal rate of procaine hydrolysis by a factor of up to 10 with no change in the Michaelis constant can be taken as clear proof of a genuine enzyme increase.

An isolated increase in the smooth membranes of the endoplasmic reticulum without ribosomes in the liver cells of rats, rabbits, and dogs after administration of phenobarbitone – although histologically unidentifiable – could be surprisingly well demonstrated with the electron microscope; this agrees with the biochemical findings. Similar structural changes were observed after administration of tolbutamide (Rastinone®) and nikethamide (Coramine®) using electron microscopy.

Possible Modes of Binding of Formaldehyde in Urine

N. Riethbrock, Hamburg (Germany)

Formaldehyde appears in the urine of cats and dogs after they have been fed with sea fish. Additional formaldehyde is liberated on acid hydrolysis of ammoniacal 24 hr. specimens of urine. Besides this reversibly bound formaldehyde, there is some formaldehyde which is irreversibly bound (formaldehyde determination with chromotropic acid after steam distillation).

The following reactions are of importance for the binding of formaldehyde in urine: 1. reactions between formaldehyde and amino or imino groups; 2. reactions between formaldehyde and mercapto groups; 3. reactions between formaldehyde and phenols.

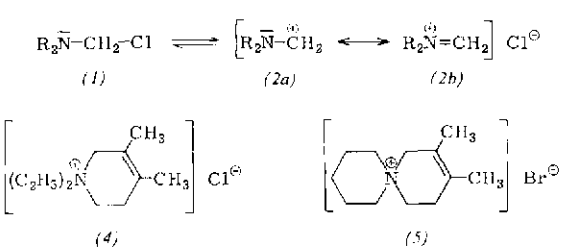
At normal urinary pH values, formaldehyde combines principally with urea. The stability of the formaldehyde-urea compound in the urine depends on the hydrogen ion concentration as well as on the relative amounts of the reactants. Since the urea concentration varies in different species within wide limits, there is either a rise or a fall in the hydrolysis curve in the pH range from 5 to 2.

Aliphatic α-amino acids without a hetero atom, basic amino acids, ammonia, methylamine, and dimethylamine react with formaldehyde forming easily hydrolysed compounds. The compounds of formaldehyde with mercapto groups, e.g. in the amino acids cysteine and methionine, can be only partially dissociated by mineral acids in strongly acid media. Too strong acidification of the urine leads to the combination of formaldehyde with phenols. The color reaction of formaldehyde and 1,8-dihydroxynaphthalene-3,6-disulfonic acid with a specific absorption maximum at 578 mμ dissappears and simultaneously a broad absorption max. at 500 mμ appears. [VB 707/91 IE]

German version: Angew. Chem. *75*, 690 (1963).

SELECTED ABSTRACTS

Dialkylaminomethyl halides *(1)* were induced by *H. Böhme, K. Hartke*, and *A. Müller* to react in a dienophilic manner as the immonium resonance form *(2b)* with 2,3-dimethylbutadiene *(3)*, forming quaternary Δ^3-piperideinium salts. From *(3)* and chloromethyldiethylamine, *(4)* was formed;



(1) *(2a)* *(2b)*

(4) *(5)*

(3) and *N*-bromomethylpiperidine gave *(5)*. / Chem. Ber. *96*, 607 (1963) / –Bö. [Rd 527/148 IE]

Synthesis of perfluoropropionic acid by electrochemical fluorination of 2,2,3,3-tetrafluoro-1-propanol *(1)* is reported by *S. Nagase, H. Baba*, and *R. Kojima*. Electrolysis of *(1)* in anhydrous HF under nitrogen at 5–6 °C with an anode current density of 1.1×10^{-2} to 2.7×10^{-2} amps/cm² gave the acid in yields of up to 52 mole-%. The yield rose with cell temperature and anode current density. Some trifluoroacetic acid was formed as by-product, particularly at higher temperatures. Fluorine probably attacks the α-carbon atom of the fluoro-alcohol; this step is followed by dehydrofluorination with subsequent fluorination of the fluorocarbonyl fluoride to give the perfluorocarbonyl fluoride. Electrochemical fluorination of 2,2,3,3-tetrafluoropropionic acid gave only traces of the perfluorinated compound. / Bull. chem. Soc. Japan *36*, 29 (1963) / –Ma. [Rd 564/158 IE]

Oriented overgrowth of polyethylene on polyoxymethylene was observed by *J. Willems* as the first case of overgrowth involving two high molecular-weight materials. Any overgrowths involving high molecular-weight guests found so far occurred exclusively on crystals of low molecular-weight substances as hosts. If the surface of a small plate obtained by compression of granular polyoxymethylene is heated to 120 °C and treated with an approximately 0.2 % solution of polyethylene (Marlex, mol. wt. 105000) in *p*-xylene, needle-

like or fibrous, frequently bent clusters crystallize out. Their axes of length are parallel and lie vertically to the direction in which the longitudinal axes of overgrown pentachlorophenol crystals would be oriented. Overgrowths on stretched polyoxymethylene films gave an orientation parallel to the direction of stretching and thus to the axis of the polyoxymethylene molecules for the axes of length of pentachlorophenol crystals, while the longitudinal axes of polyethylene crystallites were oriented vertically to the direction of stretching. / Naturwissenschaften *50*, 92 (1963) / –Ho. [Rd 565/159 IE]

Diffuse reflectance spectra of adsorbed iodine. The color of iodine in solvents is explained nowadays as being due to the formation of molecular complexes of solvent molecules with iodine, which acts as electron-acceptor. These complexes show a specific electron-transfer band; moreover, the absorption spectrum of free iodine is displaced to a greater or lesser extent toward shorter wavelengths. Finally, a concentration-dependent band is also observed, which may be assigned to associated I_4 molecules. *G. Kortüm* and *H. Koffer* have now demonstrated the occurrence of this type of electron-transfer complex of iodine for iodine adsorbed on solid substances by using diffuse reflectance spectra. Measurements on rigorously dried Aerosil as adsorbent show that the iodine is bound relatively firmly by electron-transfer to any free excess silanol groups and relatively loosely to the siloxane groups at the surface. Moreover, here they also observed association to the I_4 molecule, which can be interpreted as a self-contained electron-transfer complex in which I_2 acts both as donor and acceptor. The heat of formation of I_4 was evaluated from the temperature-dependence of the equilibrium constant, and the heat of adsorption of the iodine bound to the siloxane groups was determined from the temperature-dependence of the adsorption isotherm. / Ber. Bunsenges. physik. Chem. *67*, 67 (1963) / –Km. [Rd 506/145 IE]

BOOK REVIEWS

Encyclopedia of Plant Physiology, edited by *W. Ruhland*, Vol. VIII: Nitrogen Metabolism, edited by *K. Mothes*. Springer-Verlag, Berlin-Göttingen-Heidelberg 1958. 1st Edit. XXI plus 1310 pp., 50 figures. Price DM 286.– (about $ 72.–).

The extensive volume VIII of the 18-volume Encyclopedia of Plant Physiology deals with nitrogen metabolism, one of the central problems of the physiology and biochemistry of plants. Thirty-four authors from eight countries report in detail in 44 contributions on the fixation of nitrogen by plants, the biologically important forms of combined nitrogen and their assimilation, amino acid metabolism, plant peptides and proteins, their serology, and also their importance in human and animal nutrition. A fairly large number of articles is devoted to various aspects of protein and nucleic acid metabolism, as well as to the question of amino acid degradation and ammonia detoxification. Contributions on ring closures involving nitrogen, biogenic amines, alkaloids and other nitrogenous "secondary plant substances", as well as on denitrification, nitrification, and the geochemical significance of nitrogen complete the volume. Depending on the subject and who the author is, physiological or biochemical questions are emphasized. In most of the essays, as complete a treatment as possible of even the older literature is attempted, but some authors have contented themselves with a relatively short survey.

Almost five years have passed since the appearance of this volume, and it is even about seven years since the preparation of most of the articles. Naturally further, sometimes even very decisive progress has been achieved in the meantime in nearly all of the fields dealt with, especially in the realms of protein and nucleic acid metabolism, which at the moment is the object of intensive interest. Nevertheless, the extremely copious material brought together in this volume will this for quite a long time be indispensable to all working in field. Its utilization is facilitated by a very complete subject index.

E. Kessler [NB 991/39 IE]

Flammenphotometrie (Flame Photometry) by *R. Herrmann* and *C. T. J. Alkemade*, Springer-Verlag, Berlin-Göttingen-Heidelberg, 1960, 2nd edit., VIII, 395 pp., 61 illustr., cloth-bound DM 88.– (about $22. –).

This second, revised edition of the well-known book by *R. Herrmann* has appeared as a joint work with *C. T. J. Alkemade*. It has been enlarged and made more comprehensive in order to cope adequately with the abundant material collected by the authors since publication of the first edition. One welcome extension is the section on recent results of fundamental research. In view of these results, it is not surprising that so far there is no comprehensive theory of flame reactions, because the processes involved are only partially explicable in thermodynamic terms, and further investigation of these questions is called for.

The thorough and reliable descriptions of apparatus and assay methods, as well as the chapters on analytical procedures and on the recognition and limitation of error give extremely valuable assistance to the beginner. The experienced reader gets the impression of participating in an exchange of knowled gewith experts who have a really vast repertoire of practical tips. The chapter on applications of flame photometry refers, for example, to a wide variety of agricultural, medical, and industrial problems and is supplemented by an extensive literature review (766 references).

The chapter on detection limits gives a very clear presentation on the basis of current concepts regarding statistical methods; it therefore seems recommendable that in future editions, the discussion of accidental and systematic errors should be dealt with in a similar manner. It is also to be hoped that future editions will include a detailed description and evaluation of atomic absorption photometry.

This lucidly arranged and very readable book contains 61 clear illustrations as well as a flame line and band wavelength index. The increasing importance of recording instruments is reflected in the novel inclusion of 74 flame spectral curves. The book can be recommended both as a thorough introduction to the subject and as a comprehensive reference book for the practising chemist.

H. Zettler [NB 21/49 IE]

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Some new Developments in the Chemistry of Psychotherapeutic Agents

BY DR. E. JUCKER [*]

PHARMAZEUTISCH-CHEMISCHE FORSCHUNGS-LABORATORIEN SANDOZ A.-G., BASEL (SWITZERLAND)

Dedicated in friendship and admiration to Dr. W. Foerst on the occasion of his 65th birthday

I. Introduction
II. Psychotherapeutic Agents in Practical Use
  a) Neuroleptics
  b) Tranquilizers
  c) Thymoleptics
  d) Monoamine-oxidase Inhibitors
III. Recent Chemical Developments
  1. Tricyclic Psychotherapeutic Agents
  2. Quinolizine Derivatives
  3. Indole and Piperazine Derivatives
  4. Butyrophenone Derivatives
  5. Other Compounds
IV. Properties and Uses of Psychotherapeutic Agents
  1. General
  2. Neuroleptics
  3. Properties and Uses of Antidepressants or Exhilarants
  4. Properties and Uses of New Compounds with Psychotropic Activity

I. Introduction

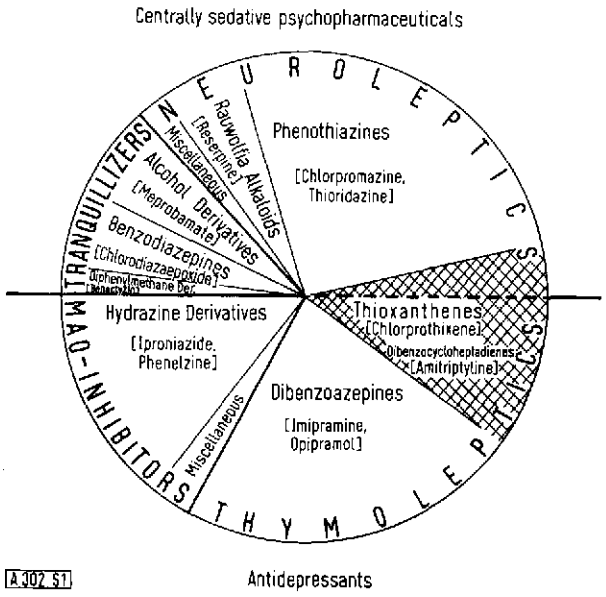
Ten years have elapsed since the introduction of chlorpromazine and reserpine for therapeutic treatment of psychic disturbances. During this period, this field has undergone a development which is practically without parallel. The inception of vast chemical, pharmacological, and clinical research has placed a whole spectrum of psychotherapeutic agents at the disposal of the physician, thus enabling him to treat even the most difficult psychic disturbances [1]. The compounds available at present can be divided, according to their activity, into two main categories: those with psychosedative and depressant activity and those with antidepressant and stimulating properties. This classification is naturally very summarical; however, it has the advantage of being significant, and it permits classification into more closely related subdivisions. The neuroleptics and the tranquilizers belong to the psychosedative preparations; the thymoleptics and monoamine-oxidase inhibitors belong to the antidepressant group. Chemically, the neuroleptics are phenothiazines (a few are also azaphenothiazines), *Rauwolfia* alkaloids, benzo-

[*] In the preparation of this manuscript, the author was given substantial support by Dr. *M. Frossard*. He assembled the extensive literature references, especially to patents. I wish to express my appreciation here for his valuable collaboration.

[1] Some reviews on psychotherapeutic agents:
O. H. Arnold, H. Gastager, and *G. Hofmann*, Pharmakologische Behandlungen in der Psychiatrie, in *H. Hoff*: Therapeutische Fortschritte in der Neurologie und Psychiatrie. Urban und Schwarzenberg, Vienna and Innsbruck 1960, p. 305;
J. Delay and *P. Deniker*: Méthodes chimiothérapiques en psychiatrie, les nouveaux médicaments psychotropes. Masson et Cie, Paris 1961;
E. F. Domino, Human Pharmacology of Tranquilizing Drugs, Clinical Pharmacology and Therapeutics *3*, 599 (1962);
H. Hoff et al., Wiener med. Wschr. *110*, 712 (1960);
A. Jenni and *A. Pletscher*, Monoaminoxydase-Hemmer, Schweiz. Apoth. Ztg. *100*, 177 (1962);
J. Knabe, Über psychotrop wirksame Substanzen, Mitt. dtsch. pharmaz. Ges. *32*, 25 (1962);
F. Labhardt, Die Bedeutung der modernen medikamentösen Therapie für die psychiatrische Klinik und Praxis, Schweiz. med. Wschr. *89*, 76, 105 (1959);

quinolizines, butyrophenone derivatives, indole or piperazine derivatives, thioxanthenes, or dibenzocycloheptadienes. The last two overlap into the field of thymoleptics. Tranquilizers are derivatives of diphenylmethane and aliphatic alcohols and compounds of the chlorodiazaepoxide class.

The thymoleptics with antidepressant activity are derivatives of dibenzoazepine or hydrazino or amino compounds. The latter are monoamine-oxidase inhibitors. In Scheme 1,we have attempted to classify the most



Scheme 1. Synopsis of psychotherapeutic agents.
MAO = Monoamine-oxidase.

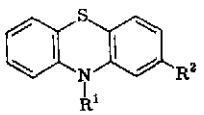
important psychotherapeutic agents in current use into a system that takes both the chemical and the medical aspects into account and permits recognition of the gradual transition of effects from psychosedative to antidepressant activity.

II. Psychotherapeutic Agents in Practical Use

a) Neuroleptics

The great success of chlorpromazine and reserpine has resulted in tremendous interest in phenothiazine derivatives and reserpine analogues. In the last few years, thousands of new phenothiazine compounds have been synthesized and tested pharmacologically and to some extent clinically; this has resulted in the development of a considerable number of practically applicable drugs. Several characteristic representatives are shown in Table 1.

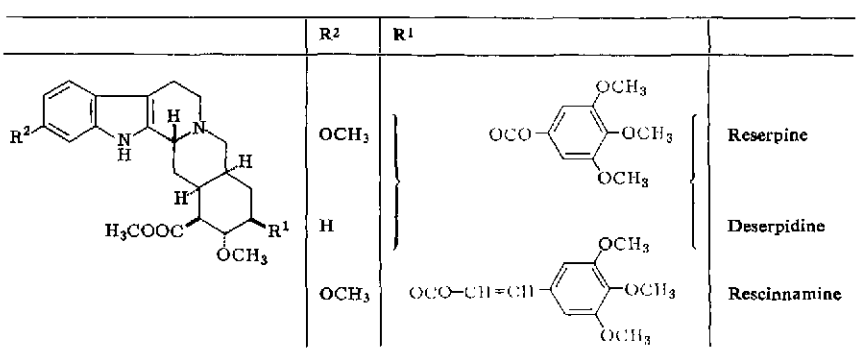
Table 1. Phenothiazine derivatives in practical use.



	R^1	R^2
Chlorpromazine	$-(CH_2)_3-N(CH_3)_2$	Cl
Trifluoperazine	$-(CH_2)_3-N$ piperazine $-N-CH_3$	CF_3
Acetophenazine	$-(CH_2)_3-N$ piperazine $-N-(CH_2)_2-OH$	$COCH_3$
Thioridazine	$-(CH_2)_2-$ piperidine $-CH_3$	SCH_3

It is apparent that all phenothiazines with psychotropic activity have several structural features in common: a monovalent functional substituent in position 2 and a basic side chain attached to the nitrogen of the tricyclic system, the basic grouping usually being separated from the ring system by three methylene groups. Azaphenothiazines are also constructed on this principle; in this series, for example, prothipendyl has been used as a mild psychotherapeutic drug.

Table 2. *Rauwolfia* alkaloids of the reserpine type in practical use.



	R^2	R^1	
	OCH_3	3,4,5-trimethoxybenzoyloxy	Reserpine
	H	3,4,5-trimethoxybenzoyloxy	Deserpidine
	OCH_3	3,4,5-trimethoxycinnamoyloxy	Rescinnamine

In spite of considerable experimental difficulties, the reserpine analogues were thoroughly investigated by synthesis or partial synthesis. However, so far no psychotherapeutic agents have resulted from this work, so that today only *Rauwolfia* alkaloids of the reserpine type are in use as neuroleptics, especially in mixtures. These are summarized in Table 2.

[1] Continued from previous page

H. Lieser, Moderne Pharmakotherapie in der Psychiatrie, Med. Klin. *57*, 90 (1962);

H. Linke, Psychotrope Substanzen, Münchn. med. Wschr. *102*, 995, 1069 (1960);

A. Pletscher, Zur Pharmakologie der modernen Psychopharmaka, Praxis *50*, 1322 (1961);

W. Pöldinger, Über die „antipsychotische Wirkung" verschiedener Psychopharmaka, Therap. Umschau *20*, 143 (1963);

E. Schenker and *H. Herbst*, Phenothiazine und Azaphenothiazine als Heilmittel, in *E. Jucker:* Fortschritte der Arzneimittelforschung. Birkhäuser, Basel and Stuttgart 1963, Vol. 5, p. 269;

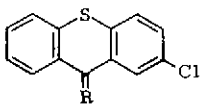
M. Taeschler and *E. Schlager*, Psychopharmaka, Schweiz. Apoth. Ztg. *99*, 683 (1961); *100*, 61 (1962);

H. Weidmann, Zur Pharmakologie psychotroper Wirkstoffe, Schweiz. Arch. Tierheilkunde *103*, 191 (1961).

Recently, investigations in this field seem to have stopped altogether. The newest developments lie in the direction of totally synthetic, simpler compounds which will be discussed later.

The success of phenothiazine derivatives in the treatment of psychic disturbances suggested substitution of the phenothiazine tricyclic system with analogous three-ring systems. A series of thioxanthene derivatives resulted (Table 3). Their activity is strongly reminiscent of the phenothiazine neuroleptics, but they possess some characteristics of the thymoleptics with antidepressant activity. This gradual transition from one type of activity into (apparently) the opposite is also shared by several phenothiazine derivatives, *e.g.* thioridazine.

Table 3. Thioxanthene derivatives.

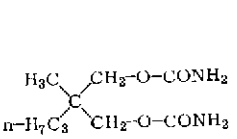


Chlorprothixen
R: $=CH-(CH_2)_2-N(CH_3)_2$
Clopenthixol
R: $=CH-(CH_2)_3-N$ $N-(CH_2)_2-OH$

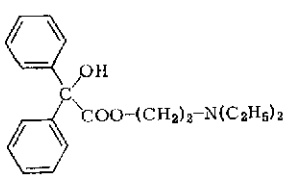
b) Tranquilizers

Whereas the neuroleptics find use primarily in severe psychic disturbances, the very thoroughly investigated group of compounds known as tranquilizers possesses properties that make the compounds of this group particularly valuable in mild disturbances of the psychic equilibrium. These disturbances are especially frequent today, and for this reason tranquilizers are used extensively. They are derived primarily from aliphatic diols or from diphenylmethane. Recently, derivatives of benzdiazepine have been added. In view of this, we restrict ourselves to the formulae of the three substances shown in Table 4.

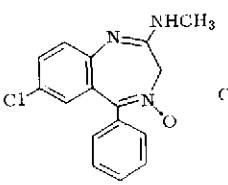
Table 4. Three typical tranquilizers.



Meprobamate



Benactyzine

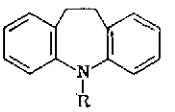


Chlorodiazepoxide

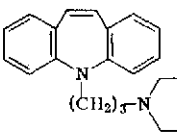
c) Thymoleptics

One obvious modification in the phenothiazine series involved replacement of the sulfur by an ethylene group while retaining the basic side chain attached to the nitrogen atom in the ring. Thus, several years ago, there appeared the first representative of a new type of drug having an activity which, in contrast to the neuroleptics, was characterized by considerable antidepressant and stimulant properties. Imipramine, developed in the Geigy laboratories, is still the most important substance in this group and has found considerable use because of its activity and excellent tolerance. Table 5 shows imipramine and its analogues.

Table 5. Imipramine and analogous thymoleptics.



Imipramine
R= $-(CH_2)_3-N(CH_3)_2$
Demethylimipramine
R= $-(CH_2)_3-NH-CH_3$

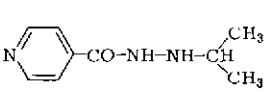


Opipramol (Ensidone® in U.S., Insidone® in Europe)

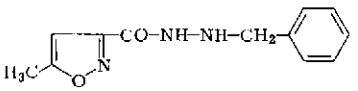
d) Monoamine-oxidase Inhibitors

In the early fifties, during investigations on isoniazide and similar tuberculostatics in the laboratories of Hoffmann-LaRoche in Basel, *Zeller* and co-workers observed that certain hydrazine derivatives exert a strong stimulant and antidepressant activity on depressed patients. This observation led to the initiation of work on hydrazine derivatives, with the result that there are now several hydrazines and recently also amines with antidepressant and stimulant activity. These preparations are characterized by strong inhibition of the enzyme monoamine-oxidase and are therefore summarized under the collective term of monoamine-oxidase inhibitors.

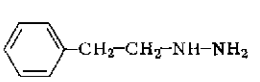
Table 6. Monoamine-oxidase inhibitors.



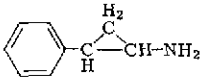
Iproniazide



Isocarboxazide



Phenelzine



Tranylcypromine

III. Recent Chemical Developments

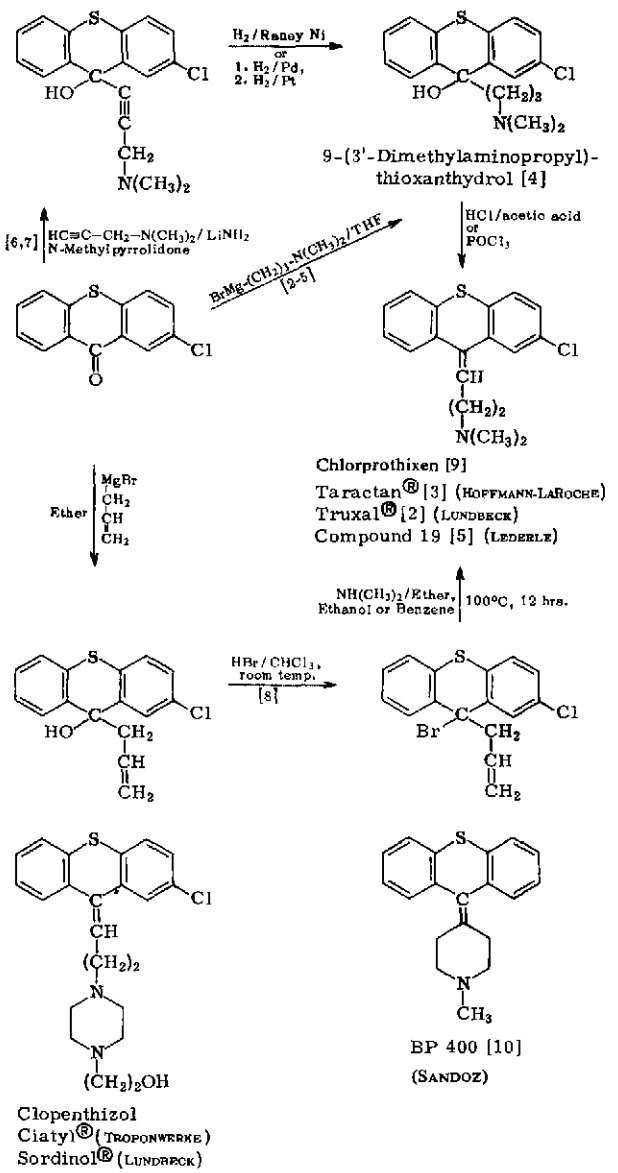
The treatment of psychic disturbances has undergone a fundamental change during the ten years that have elapsed since the introduction of chlorpromazine and reserpine. Many patients who were previously hospitalized have been discharged to ambulatory care, and others, who remained institutionalized, were rescued from an almost vegetative existence, and admitted to work therapy. As expected, this gratifying development has caused enormous intensification of chemical, pharmacological, and clinical research in the field of psychotherapeutic agents, with the result that numerous (some entirely new) ring systems were developed of which various prototypes are already in clinical use or have been tested clinically. We have attempted to depict this development in the discussion which follows, with

emphasis on the chemical aspects, especially with regard to the synthesis of the compounds. We will again discuss the thioxanthenes and dibenzazepines briefly, since studies in the field of these compounds have not yet reached the status of those of the phenothiazines and reserpine derivatives, as new preparations are still being subjected to clinical trial.

1. Tricyclic Psychotherapeutic Agents

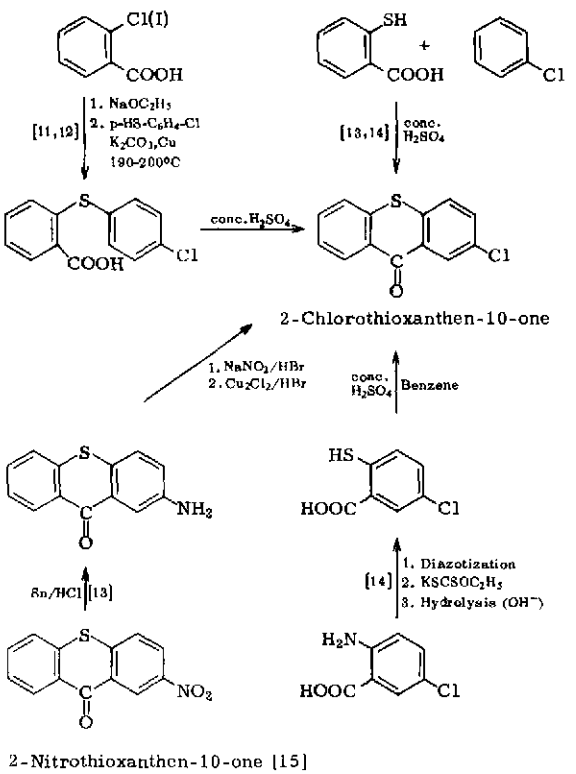
a) Thioxanthene Derivatives

Although formerly thioxanthene derivatives were used exclusively as anthelminthics, several years ago it became possible to prepare compounds with psychotropic activity. In the first syntheses of this type, it seemed desirable to introduce substituents resembling those present in known phenothiazine neuroleptics into the tricyclic system. Thus, for example, the chlorpromazine analogue, chlorprothixen, resulted. A typical mode of synthesis leading to compounds of this type is shown in Scheme 2. If the dimethylaminopropane side chain is replaced by piperazines or *N*-methylpiperidine, compounds of the clopenthizol or BP 400 type are obtained.



Scheme 2. Synthesis of thioxanthenes with an aminopropane side chain. THF = tetrahydrofuran.

Practically all the syntheses of thioxanthene psychotherapeutics start out from thioxanthen-10-one or from 2-chlorothioxanthen-10-one. The synthesis of the latter important starting material is shown in Scheme 3.



Scheme 3. Synthesis of 2-chlorothioxanthen-10-one.

It has already been mentioned that all the psychotherapeutic agents of the aromatic tricyclic type used in practice have a basic nitrogen function which is always separated by three $-CH_2-$ groups from the three-ring system. In order to investigate the relationship of structure to function, it was of interest to reduce this to two $-CH_2-$ groups. Since the Grignard reaction normally used for the synthesis of such compounds fails with aminoethylene compounds, *Ebnöther*, *Jucker*, and

[2] *P. V. Petersen*, *N. Lassen*, *T. Holm*, *R. Kopf*, and *I. Moller-Nielsen*, Arzneimittel-Forsch. *8*, 395 (1958).

[3] Swiss Pat. 349617, Hoffmann-LaRoche.

[4] U.S. Pat. 3047580, Merck & Co., Inc.

[5] *G. E. Bonvicino*, *H. G. Arlt jr.*, *K. M. Pearson*, and *R. A. Hardy jr.*, J. org. Chemistry *26*, 2383 (1961).

[6] *W. Ried* and *J. Schönherr*, Chem. Ber. *93*, 1870 (1960).

[7] French Pat. 1288023, Hoffmann-LaRoche.

[8] Belg. Pat. 585338, Kefalas A/S; see also Danish Pat. 88606, 88974; Chem. Abstr. *55*, 5536g, 21149a (1961).

[9] U.S. Pat. 2996503, 3046283, Merck & Co., Inc.

[10] Belg. Pat. 603154, Sandoz AG.

[11] *N. B. Mahishi*, *P. B. Sattur*, and *K. S. Nargund*, J. Karnatak. Univ. *2*, 50 (1957); Chem. Abstr. *53*, 14102b (1959).

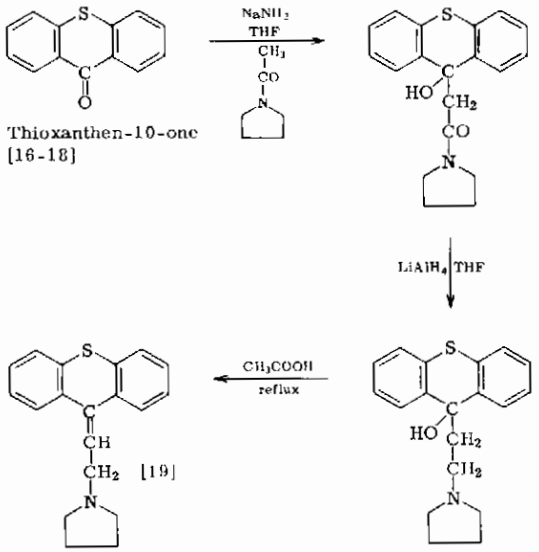
[12] Brit. Pat. 803401, Merck & Co., Inc.

[13] *H. Gilman* and *J. W. Diehl*, J. org. Chemistry *24*, 1914 (1959).

[14] Brit. Pat. 863699, Chas. Pfizer.

[15] *E. Amstutz* and *C. Neumoyer*, J. Amer. chem. Soc. *69*, 1925 (1947).

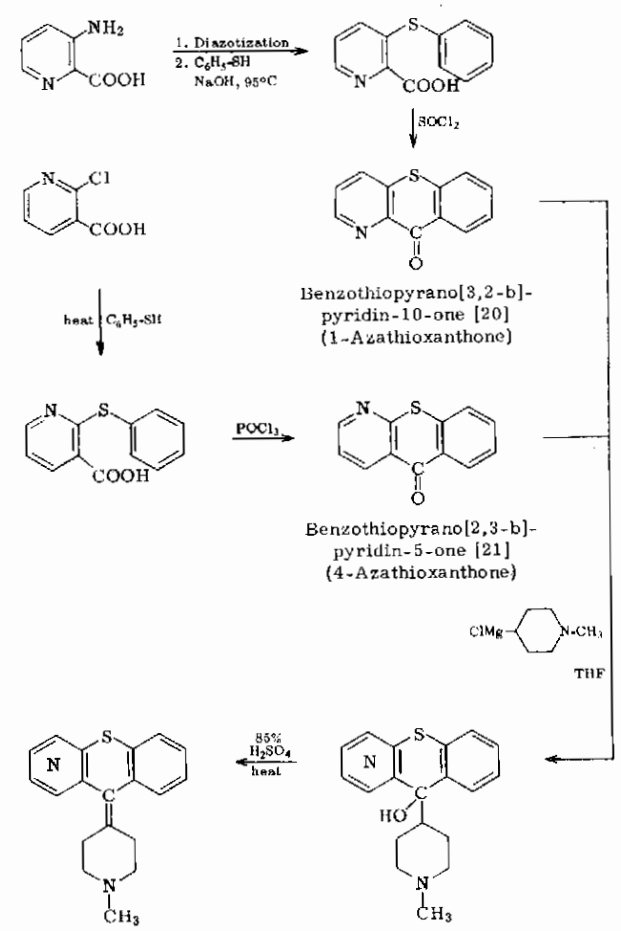
Stoll developed a new procedure which led to the desired "short-chain" substances (Scheme 4).



Scheme 4. Synthesis of thioxanthenes with aminoethane side chain. THF = tetrahydrofuran.

b) Benzothiopyranopyridines (Azathioxanthene Derivatives)

Observations on interesting effects of different thioxanthenes prompted the synthesis of analogous compounds.

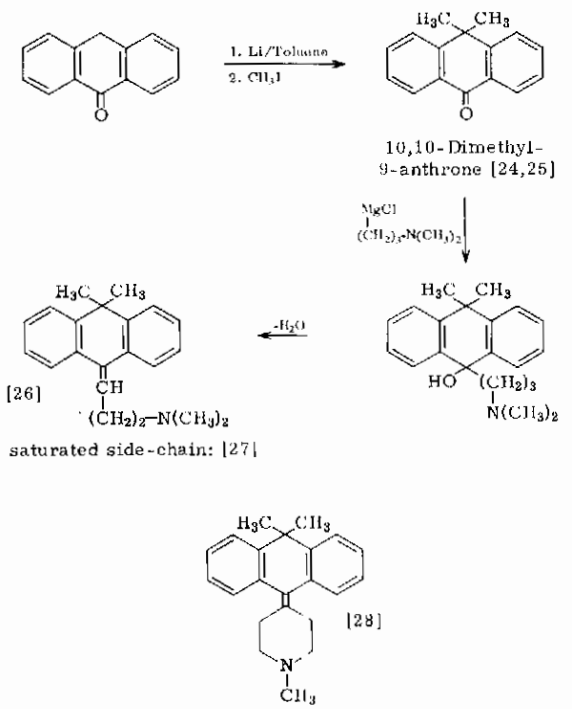


Scheme 5. Synthesis of azathioxanthene derivatives.

What seemed to be of particular interest in this connection was replacement of the benzene ring in the thioxanthene tricyclic system by a pyridine ring. *Jucker* and coworkers synthesized several such 1- or 4-azathioxanthene derivatives. The preparation of AP 800 is illustrated as an example in Scheme 5.

c) 10,10-Dialkyl-9-anthrone Derivatives

The psychotropic and allied effects of the phenothiazines are also present in derivatives of 10,10-dialkylanthrone which are structurally analogous. These compounds differ from those already mentioned in that they do not contain any hetero atoms. This is interesting, because the physiological effects of these compounds are not materially different from those of the phenothiazines and thioxanthenes. Their synthesis is outlined in Scheme 6.



Scheme 6. Synthesis of 10,10-dialkyl-9-anthrone derivatives.

[16] *J. H. Ziegler*, Ber. dtsch. chem. Ges. *23*, 2469 (1890).

[17] *C. Graebe* and *O. Schulthess*, Liebigs Ann. Chem. *263*, 1 (1891).

[18] *F. Mayer*, Ber. dtsch. chem. Ges. *42*, 1132 (1909).

[19] Belg. Pat. 608053, Sandoz AG.

[20] *S. Kruger* and *F. G. Mann*, J. chem. Soc. (London) *1954*, 3905.

[21] *F. G. Mann* and *J. A. Reid*, J. chem. Soc. (London) *1952*, 2057.

[22] Belg. Pat. 601668, Sandoz AG.

[23] Belg. Pat. 611216, Sandoz AG.

[24] *F. Hallgarten*, Ber. dtsch. chem. Ges. *21*, 2508 (1888).

[25] *K. H. Meyer* and *H. Schlösser*, Liebigs Ann. Chem. *420*, 126 (1920).

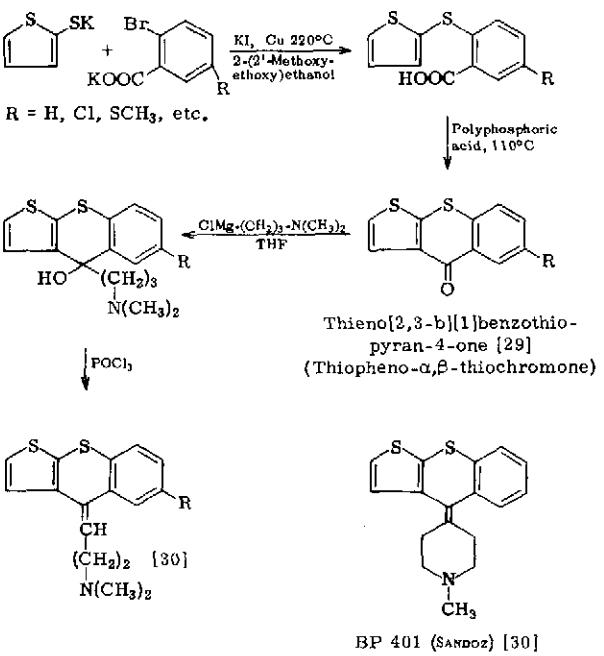
[26] Belg. Pat. 608253, 608254, Kefalas A/S.

[27] French Pat. 1278 M, Belg. Pat. 601168, Geigy AG.

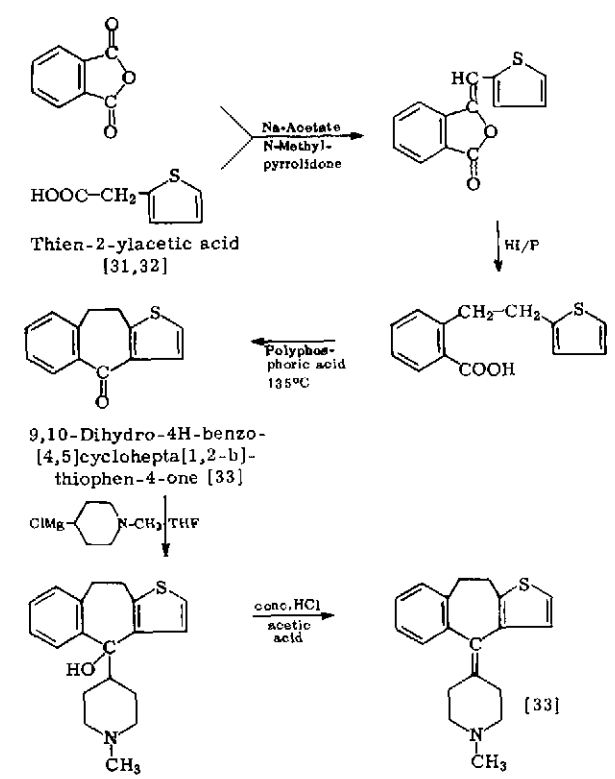
[28] Swiss Patent Appl., Sandoz AG.

d) Tricyclics Containing Thiophene

After the effects of various thioxanthene derivatives became known, it was considered relevant that thiophene might replace a benzene ring in this or analogous ring skeletons. The parent compound of this series was already prepared in 1937 by *Steinkopf*, *Schmitt*, and *Fiedler* [29]. The synthesis of substituted products was accomplished by *Renz*, *Bourquin*, and co-workers (Scheme 7).



Scheme 7. Synthesis of thieno[2,3-*b*] [1] benzothiopyrans.

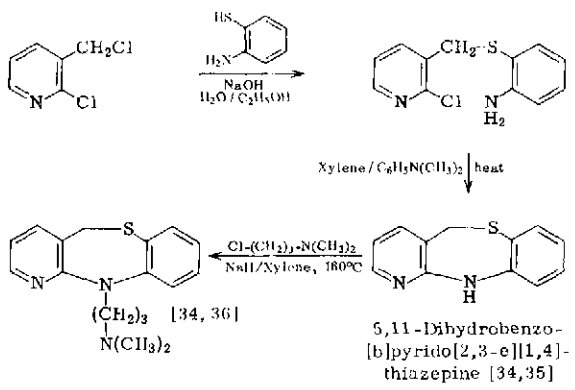


Schema 8. Synthesis of a dihydrobenzocycloheptathiophene.

Another three-ring system containing thiophene was obtained in our own laboratories from dibenzocycloheptadiene (*Ebnöther*, *Jucker*, *Stoll*, and *Bastian*). The synthesis which leads to this interesting compound is quite complicated and proceeds along the course outlined in Scheme 8.

e) Azahomophenothiazines

By modification of typical phenothiazine psychotherapeutic agents, derivatives of a new ring system, *viz.* 5,11-dihydrobenzo[*b*]pyrido[2,3-*e*] [1,4] thiazepine,were recently synthesized. The rather complicated synthesis (shown in Scheme 9) permitted the preparation of various chlorpromazine analogues and comparison of their activity with that of corresponding substances from the phenothiazine and azaphenothiazine series.



Scheme 9. Synthesis of 5,11-dihydrobenzo[*b*]pyrido[2,3-*e*] [1,4]-thiazepine derivatives.

f) Homothioxanthenes

By modification of thioxanthene, the previously unknown compound 6*H*-dibenzo[*b*,*e*]thiepine was synthesized in our laboratory [37]. The same basic structure was also synthesized recently by *Protiva* et al. [38], *Stach* et al. [39], and *Winthrop* et al. [40]. The preparation of a typical representative of this new series is illustrated in Seheme 10.

[29] *W. Steinkopff*, *H. F. Schmitt*, and *H. Fiedler*, Liebigs Ann. Chem. *527*, 237 (1937).

[30] Belg. Pat. 616813, Sandoz AG.

[31] *F. F. Blicke* and *M. F. Zienty*, J. Amer. chem. Soc. *63*, 2945 (1941).

[32] *F. F. Blicke* and *F. Leonard*, J. Amer. chem. Soc. *68*, 1934 (1946); U.S. Pat. 2533084, University of Michigan.

[33] Swiss Patent Appl., Sandoz AG.

[34] *F. Gadient*, *E. Jucker*, and *A. Lindenmann*, Helv. chim. Acta *45*, 1860 (1962).

[35] Belg. Pat. 602727, Sandoz AG.

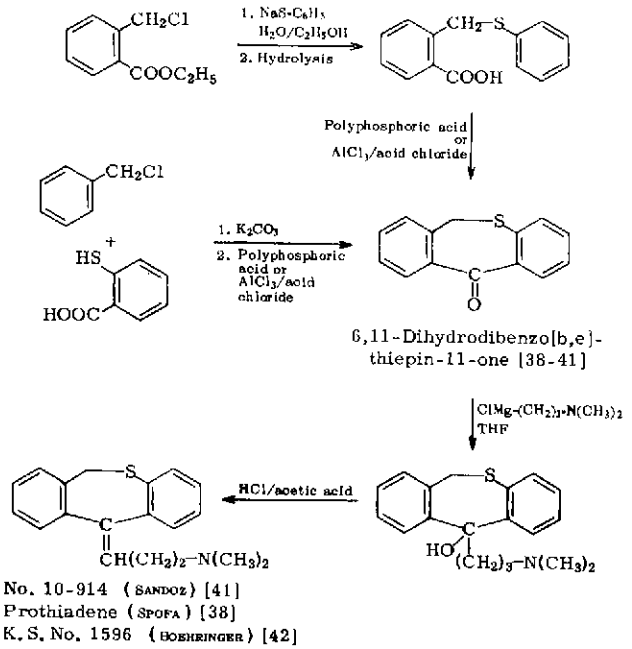
[36] Belg. Pat. 602728, Sandoz AG.

[37] This compound was described for the first time by the author in a plenary lecture at the Indian Science Congress, January 1962, in Cuttack, India. See *E. Jucker*, J. Sci. ind. Res. (India) Section A *21*, 415 (1962).

[38] *M. Protiva*, *M. Rajšner*, *V. Seidlová*, *E. Adlerová*, and *Z. J. Vejdělek*, Experientia *18*, 326 (1962); Belg. Pat. 618591, Spofa N. P.

[39] *K. Stach* and *H. Spingler*, Angew. Chem. *74*, 31 (1962); Angew. Chem. internat. Edit. *1*, 50 (1962); Mh. Chem. *93*, 889 (1962).

[40] *S. O. Winthrop*, *M. A. Davis*, *F. Herr*, *J. Stewart*, and *R. Gaudy*, J. med. pharmac. Chem. *5*, 1207 (1962).



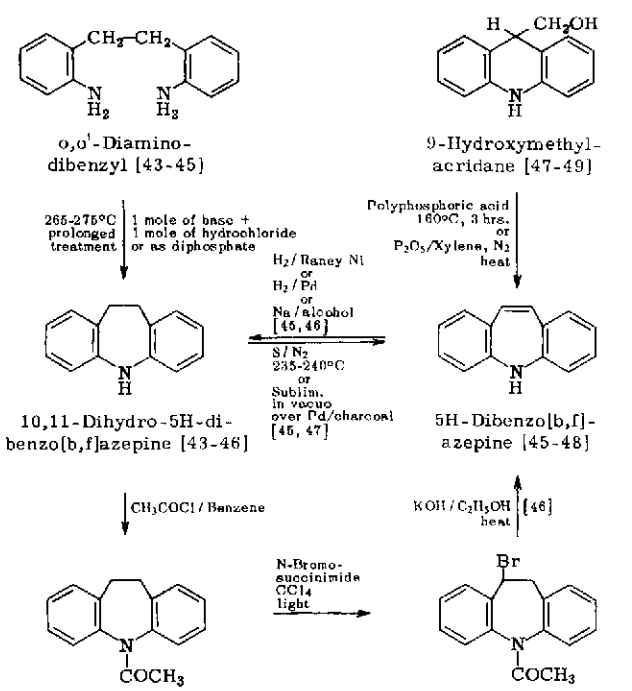
6,11-Dihydrodibenzo[b,e]-thiepin-11-one [38-41]

No. 10-914 (SANDOZ) [41]
Prothiadene (SPOFA) [38]
K.S. No. 1596 (BOEHRINGER) [42]

Scheme 10. Synthesis of 6 *H*-dibenzo[*b*,*e*]thiepines.

g) Dibenzazepines

As already mentioned, the modification of the phenothiazine structure to the dibenzazepine tricyclic system, accomplished in the Geigy laboratories in Basel, is a fundamental and important advance in that compounds were obtained which were no longer neuroleptics but were characterized by their thymoleptic, *i.e.* antidepressant and stimulating, properties. The parent compound can be obtained by different pathways, as shown in Scheme 11, and then not only as unsaturated 5*H*-dibenzo[*b*,*f*]azepine but also as the saturated compound 10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine.



o,o'-Diamino-dibenzyl [43-45]

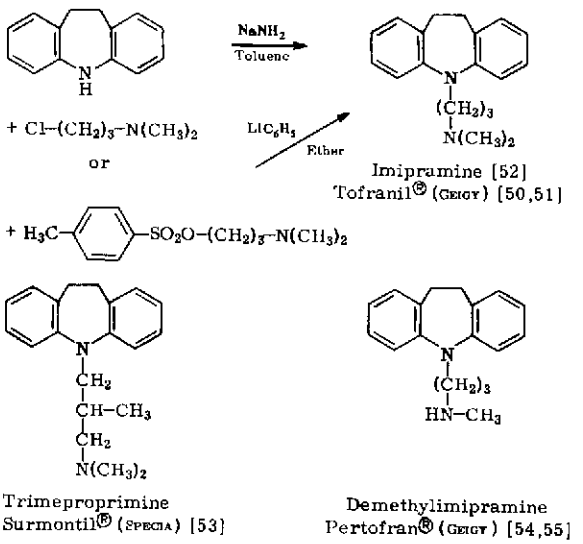
9-Hydroxymethyl-acridane [47-49]

10,11-Dihydro-5H-dibenzo[b,f]azepine [43-46]

5H-Dibenzo[b,f]-azepine [45-48]

Scheme 11. Synthesis of 5 *H*-dibenzo[*b*,*f*]azepine and its 10,11-dihydro derivative.

The most important compound of the series viz. imipramine, as well as its metabolic product demethylimipramine, was prepared by *Schindler* and *Häfliger* by the method illustrated in Scheme 12.

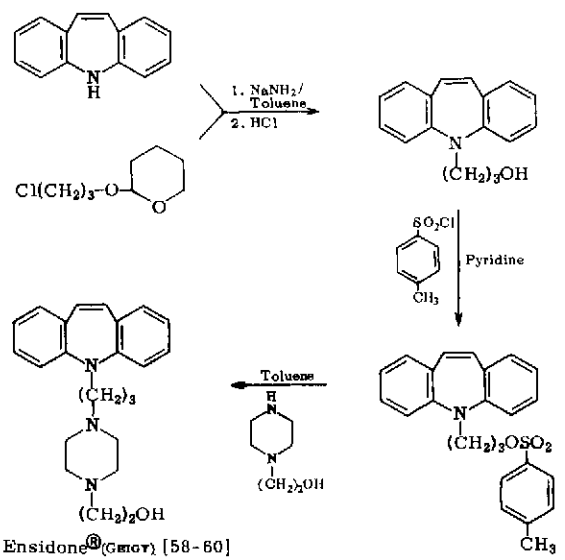


Imipramine [52]
Tofranil® (GEIGY) [50,51]

Trimeproprimine
Surmontil® (SPECIA) [53]

Demethylimipramine
Pertofran® (GEIGY) [54,55]

Scheme 12. Synthesis of dihydrodibenzazepine derivatives.



Ensidone® (GEIGY) [58-60]

Scheme 13. Synthesis of Ensidone®.

[41] *F. Gadient, E. Jucker,* and *A. Lindenmann,* Helv. chim. Acta *45,* 1860 (1962); Belg. Pat. 607503, Sandoz AG.

[42] *K. Stach* and *F. Bickelhaupt,* Mh. Chem. *93,* 896 (1962).

[43] *J. Thiele* and *O. Holzinger,* Liebigs Ann. Chem. *305,* 96(1899).

[44] U.S. Pat. 2764580, Geigy AG.

[45] *R. Huisgen, E. Laschtuvka,* and *F. Bayerlein,* Chem. Ber. *93,* 392 (1960).

[46] *W. Schindler* and *H. Blattner,* Helv. chim. Acta *44,* 753 (1961).

[47] *P. N. Craig, B. N. Lester, A. J. Saggiomo, C. Kaiser* and *C.L. Zirkle,* J. org. Chemistry *26,* 135 (1961).

[48] *E. D. Bergman* and *M. Rabinovitz,* J. org. Chemistry *25,* 827 (1960).

[49] *A. Campbell* and *E. N. Morgan,* J. chem. Soc. (London) *1958,* 1711.

[50] *W. Schindler* and *F. Häfliger,* Helv. chim. Acta *37,* 472 (1954).

[51] U.S. Pat. 2554736, Geigy AG.

[52] U.S.S.R. Pat. 137520, *V. G. Yashunskii, M. N. Shchukina, V. G. Ermolaeva,* and *O. I. Sanoilova*; Chem. Abstr. *56,* 464b (1962).

[53] *P. A. Lambert* and *J. Guyotat,* Presse méd. *69,* 1425 (1961).

[54] *J. R. Gillette, J. V. Dingell, F. Sulser, R. Kuntzman,* and *B. B. Brodie,* Experientia *17,* 417 (1961).

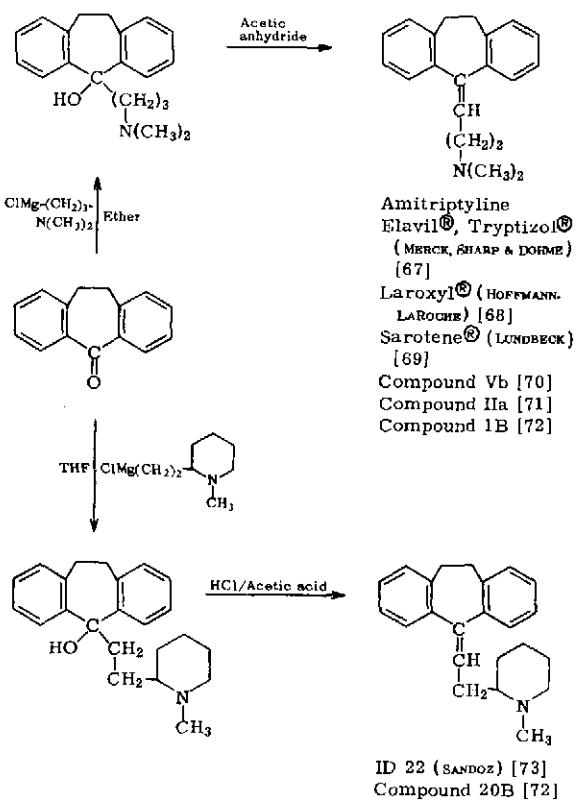
[55] French Pat. 796 M, Geigy AG.

Recently the piperazine side chain has been successfully linked to the dibenzazepine nucleus in the Geigy laboratories. The synthesis of this compound (Ensidone®) is shown in Scheme 13. For modes of synthesis of dimethylaminopropyldibenzazepine, see [56,57].

h) Dibenzosuberone Derivatives

Substitution of C=O for the NH in the ring system of dihydrodibenzazepine results in dibenzosuberone, a valuable starting material for the preparation of psychotherapeutic agents with neuroleptic-thymoleptic properties. The synthesis of dibenzosuberone was described in the early 1950's [61–66].

Treatment of dibenzosuberone with Grignard reagents of derivatives of aliphatic amines leads, via various intermediates, to drugs of the amitriptyline type, which have proved to be of value as psychotherapeutic agents. An analogous compound with a piperidine residue was synthesized simultaneously in the research laboratories of Sandoz A.G. in Basel, and of Ayerst in the U.S.A. (Scheme 14).



Scheme 14. Synthesis of 10,11-dihydrodibenzocycloheptenes with a C—C—C—N side chain.

[56] French Pat. 1196928, Geigy AG.

[57] *P. N. Craig, B. N. Lester, A. J. Saggiomo, C. Kaiser,* and *C. L. Zirkle,* J. org. Chemistry *26,* 135 (1961).

[58] Brit. Pat. 862297, Geigy AG.

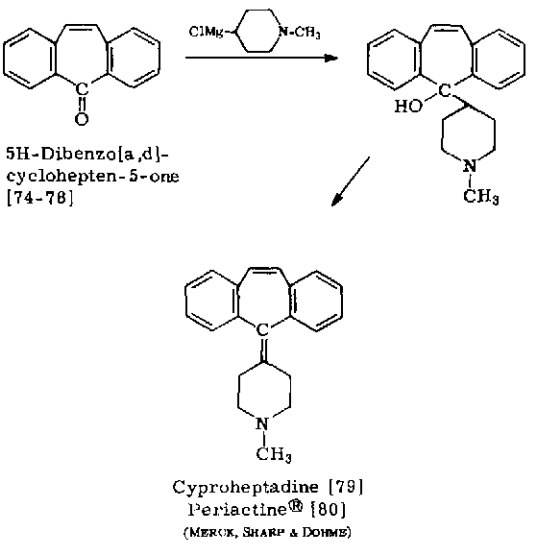
[59] French Pat. 162 M, Geigy AG.

[60] Brit. Pat. 881398, Société des usines chimiques Rhône-Poulenc.

[61] *W. Treibs* and *H. J. Klinkhammer,* Chem. Ber. *83,* 367 (1950); *84,* 671 (1951).

[62] *Van der Stelt, H. F. Harms,* and *W. T. Nauta,* J. med. pharmac. Chem. *4,* 335 (1961).

For the sake of completeness, cyproheptadine (Scheme 15) is mentioned; this compound has aroused some interest as an antihistamine. This compound will be discussed together with BP 400 and AP 800 (Sandoz A.G., Basel) since there is a relationship here between structure and physiological activity.



Scheme 15. Synthesis of cyproheptadine.

It has already been mentioned that the typical tricyclic psychotherapeutic agents have an aminopropane side chain. Shortening the distance between its basic nitrogen atom and the tricyclic skeleton results, in the case of phenothiazines, in compounds with antihistamine activity. With thioxanthenes, dibenzocycloheptadienes, and similar tricyclic compounds, the synthesis of

[63] *A. C. Cope* and *S. W. Fenton,* J. Amer. chem. Soc. *73,* 1674 (1951).

[64] *V. Mychailyszyn* and *M. Protiva,* Collect. czechoslov. chem. Commun. *24,* 3955 (1959).

[65] *T. W. Campbell, R. Ginsig,* and *H. Schmid,* Helv. chim. Acta *36,* 1489 (1953).

[66] *E. D. Bergmann, E. Fischer, D. Ginsburg, Y. Hirshberg, D. Lavie, M. Mayot, A. Pullman,* and *B. Pullman,* Bull. Soc. chim. France *18,* 684 (1951).

[67] Belg. Pat. 584061, Merck & Co., Inc.

[68] German Published Pat. Appl. 1109166, Brit. Pat. 858187, Hoffmann-La Roche.

[69] Belg. Pat. 609095, Kefalas A/S.

[70] *F. J. Villani, C. A. Ellis, C. Teichman,* and *C. Bigos,* J. med. pharmac. Chem. *5,* 373 (1962).

[71] *M. Protiva, V. Hněvsová-Seidlová, Z. J. Vejdělek, I. Jirkovský, Z. Votava,* and *J. Metyšová,* J. med. pharmac. Chem. *4,* 411 (1961).

[72] *S. O. Winthrop, M. A. Davis, G. S. Myers, J. G. Gavin, R. Thomas,* and *R. Barber,* J. org. Chemistry *27,* 230 (1962).

[73] Belg. Pat. 610038, Sandoz AG.

[74] *E. D. Bergmann, E. Fischer, D. Ginsburg, Y. Hirshberg, D. Lavie, M. Mayot, A. Pullman,* and *B. Pullman,* Bull. Soc. chim. France *18,* 684 (1951).

[75] *A. C. Cope* and *S. W. Fenton,* J. Amer. chem. Soc. *73,* 1673 (1951).

[76] *J. Rigaudy* and *C. Nedelec,* C. R. hebd. Séances Acad. Sci. *237,* 1096 (1953).

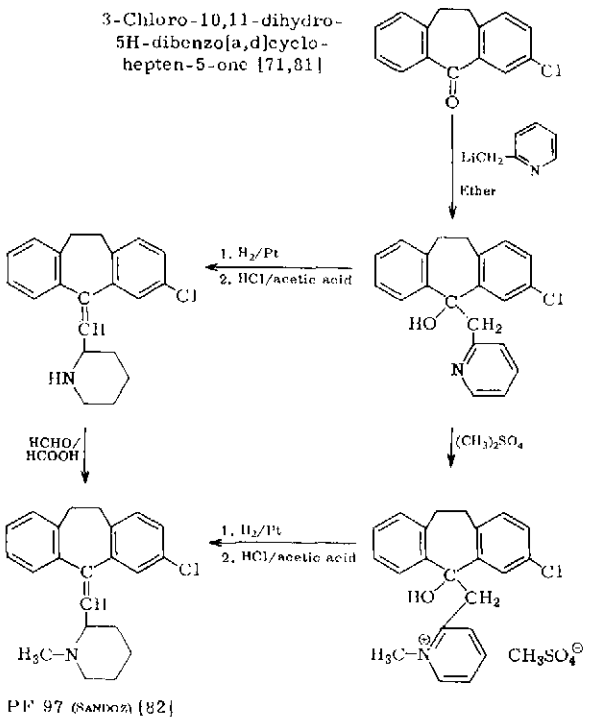
[77] *W. Treibs* and *H. J. Klinkhammer,* Chem. Ber. *84,* 671 (1951).

[78] *T. W. Campbell, R. Ginsig,* and *H. Schmid,* Helv. chim. Acta *36,* 1489 (1953).

[79] *T. Bodi, P. E. Siegler, M. Gershenfeld, E. B. Brown,* and *J. H Nodine,* Feder. Proc. *19,* 195 (1960).

[80] *E. L. Engelhardt, M. E. Christy, H. C. Zell, C. M. Dylion, M. B. Freedman,* and *J. M. Sprague,* Abstr. Papers, 141st Meeting Amer. chem. Soc. 4N (March 1962).

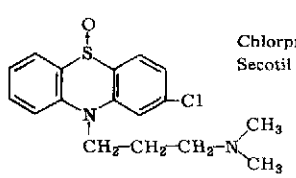
derivatives with a shortened side chain was accomplished only recently. The synthesis is difficult and cannot be carried out with Grignard reagents; it is represented in Scheme 16.



Scheme 16. Synthesis of dihydrodibenzocycloheptadienes with a C—C—N side chain.

i) Sulfoxides of Known Psychotherapeutic Agents

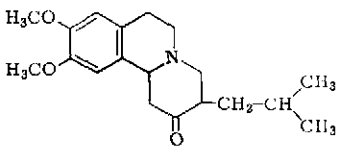
Phenothiazine psychotherapeutic drugs are metabolized to yield, among other products, sulfoxides. These compounds have effects which fit into the spectrum of the typical psychotherapeutic drugs of the neuroleptic type but are comparatively less potent. At present, Secotil® is the only one of these substances in use.



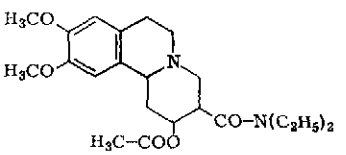
Chlorpromazine sulfoxide
Secotil® (LA SINTETICA)

2. Quinolizine Derivatives

In the last few years, the synthesis of emetine has been attempted in many ways. In the process, intermediates became available which have properties that make them useful as psychotherapeutic drugs. Of these, tetrabenazine [83] and benzquinamide [84] have been used therapeutically to date.



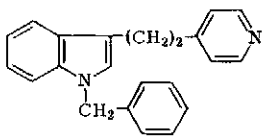
2-Oxo-3-isobutyl-9,10-dimethoxyhexahydrobenzo[*a*]quinolizine [83]
Tetrabenazine
®Nitoman (Hoffmann-La Roche)



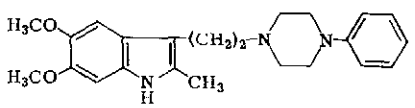
N,N-Diethyl-2-acetoxy-9,10-dimethoxyhexahydrobenzo[*a*]quinolizine-3-carboxamide [84]
Benzquinamide
®Quantril (*J.* B. Roerig and Co., Div. Chas. Pfizer & C., Inc.)
P-2647

3. Indole and Piperazine Derivatives

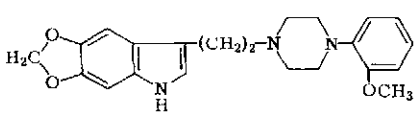
Other neuroleptics are found among the indole and piperazine derivatives. Several compounds of this series are in use in psychiatry; their extent of application, compared with that of the tricyclic compounds, is still fairly limited.



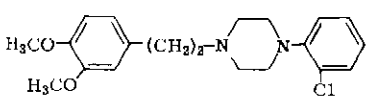
1-eBnzyl-3-[2'-(4''-pyridyl)-ethyl]indole [85]
Benzindopyrine
Pyrbenzindole
(Irwin, Neisler & Co.)



1-[2'-(5'',6''-Dimethoxy-2''-methyl-3''-indolyl)ethyl]-4-phenylpiperazine [86–88]
Oxypertine (Sterling-Winthrop)



1-[2'-(5'',6''-Methylenedioxy-3''-indolyl)ethyl]-4-(*o*-anisyl)piperazine [86—88]
®Solypertine (Sterling-Winthrop)



1-(3',4'-Dimethoxyphenethyl-4-(*o*-chlorphenyl)piperazine [89,90]
SD 218–06 (Scrat, Société Centrale de Recherches et d'Applications Techniques, Paris).

[81] *F. J. Villani, C. A. Ellis, C. Teichman,* and *C. Bigos,* J. med. pharmac. Chem. *5,* 373 (1962).

[82] Swiss Pat. Appl., Sandoz AG.

[83] *A. Brossi, H. Lindlar, M. Walter,* and *O. Schnider,* Helv. chim. Acta *41,* 119 (1958).

[84] Belg. Pat. 618741, 621895, Chas. Pfizer.

[85] *A. P. Gray* and *W. L. Archer,* J. Amer. chem. Soc. *79,* 3554 (1957); Brit. Pat. 842996, Irwin, Neisler & Co.

[86] *S. Archer, D. W. Wylie, L. S. Harris, T. R. Lewis, J. W. Schulenberg, M. R. Bell, R. K. Kulling,* and *A. Arnold,* J. Amer. chem. Soc. *84,* 1306 (1962).

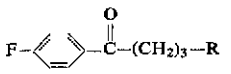
[87] *D. W. Wylie* and *S. Archer,* J. med. pharmac. Chem. *5,* 932 (1962); Feder. Proc. *21,* 322 (1962).

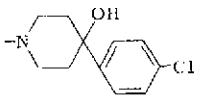
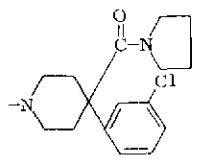
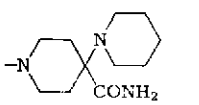
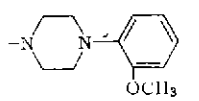
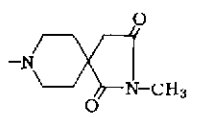
[88] Belg. Pat. 595341, Sterling Drug Inc.

4. Butyrophenone Derivatives

In the last few years, *Janssen* et al. synthesized many derivatives of butyrophenone, some of which possess psychotropic activity; a few have also found restricted practical application. The most important substances of this series are summarized in Table 7.

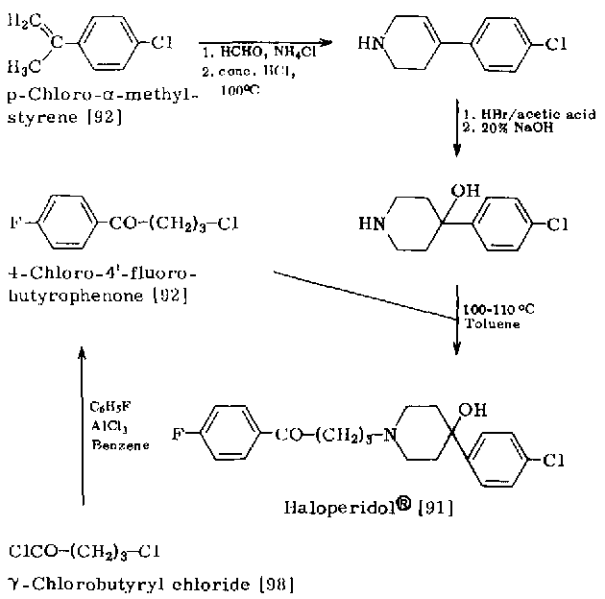
Table 7. Butyrophenone derivatives of the type



R	Name	Ref.
	4-[4'-Hydroxy-4'-(4''-chlorophenyl)-piperidino]-*p*-fluorobutyrophenone ®Haloperidol (Res. Lab. Dr. Janssen) ®Aldol (Leo, Denmark)	[91,92]
	4-[4'-Pyrrolidinocarbonyl-4'-(3''-chlorophenyl)piperidino]-*p*-fluorobutyrophenone ®Haloperidide (Res.Lab. Dr. Janssen)	[93]
	4-(4'-Carbamoyl-4'-piperidino-piperidino)-*p*-fluorobutyrophenone Dipiperone (Res. Lab. Dr. Janssen)	[94,95]
	4-[4'-(2''-Methoxyphenyl)-piperazinol]-*p*-fluorobutyrophenone ®Haloanisone (Res. Lab. Dr. Janssen)	[96]
	2-Methyl-8-(4'-*p*-fluorophenyl-4'-oxobutyl)-2,8-diazaspiro[4,5]-decane-1,3-dione FR 33 (Sandoz)	[97]

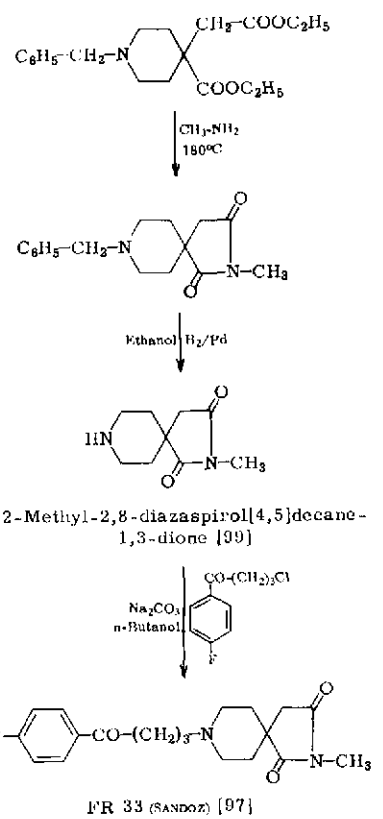
In addition, Table 7 contains FR 33, which was synthesized in the Sandoz laboratories and which has a new piperidylspirosuccinimide structure. The best known representative from the group of compounds investigated by *Janssen* is Haloperidol®, the synthesis of which is shown in Scheme 17.

FR 33 originated from an extensive series of investigations (*Jucker* and *Süess*) which were supposed to lead to the development of antispasmodics. Pharmacological testing (*Cerletti*, *Taeschler*, et al. in the Medizinisch-Biologische Abteilung of Sandoz A.G., Basel) showed, however, that some spiro compounds are extremely effective anticholinergics and that some are psychotherapeutic agents. FR 33 is a typical representative of



Scheme 17. Synthesis of Haloperidol®.

the latter group, and is also unique in clinical experiments where it exhibits antipsychotic effects which are not typical of other psychotherapeutic drugs or even of



Scheme 18. Synthesis of the butyrophenone derivative FR 33.

[89] *J. R. Boissier, C. Dumont, R. Ratouis*, and *J. Pagny*, Arch. int. Pharmacodynam. Thérap. *133*, 29 (1961).

[90] Belg. Pat. 599763, May & Baker, Ltd.

[91] *P. A. J. Janssen, C. Van de Westeringh, A. H. M. Jageneau, P. J. A. Demoen, B. K. F. Hermans, G. H. P. Van Daele, K. H. L. Schellekens, C. A. M. Van der Eycken*, and *C. J. E. Niemegeers*, J. med. pharmac. Chem. *1*, 281 (1959).

[92] Brit. Pat. 881893, inventor: *P. A. J. Janssen*.

[93] *W. K. A. Schaper, A. H. M. Jageneau, J. Huygens*, and *P. A. J. Janssen*, Med. Exp. *3*, 169 (1960).

[94] *P. A. J. Janssen*, Arzneimittel-Forsch. *11*, 819 (1961).

[95] French Pat. 1628 M, U.S. Pat. 3041344, Research Lab. Dr. C. Janssen.

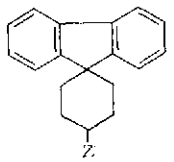
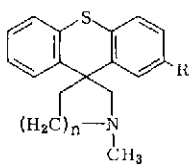
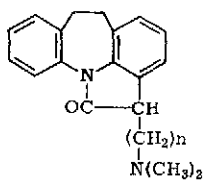
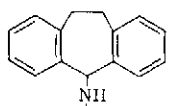
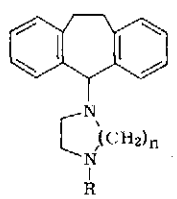
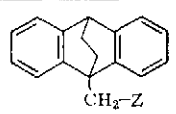
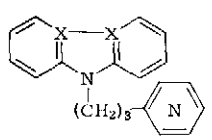
[96] *G. Daumézon, M. Audisio, C. Conte*, and *P. Huguet*, Ann. Méd. Psychol. *118* [I], 539 (1960).

[97] *E. Jucker*, J. sci. ind. Res., Sect. A, *21*, 415 (1962); Belg. Pat. 609766, Sandoz AG.

[98] *W. J. Close*, J. Amer. chem. Soc. *79*, 1455 (1957).

[99] *E. Jucker* and *R. Süess*, Arch. Pharmaz. *294*, 210 (1961); Belg. Pat. 588948, Sandoz AG.

Table 8. Compounds with anomalous side chains.

Compounds	Properties and References
 Z = NH_2, $N(CH_3)_2$, $N(C_2H_5)_2$,	Weakly analgetic, hypotensive and antihistaminic activity, comparatively high toxicity [100]
 n = 1, 2 R = H, Cl	Tranquilizer, also has bacteriostatic and fungistatic properties [101]
	Antiallergic and spasmolytic properties, weakly sedative activity [102]
	Antidepressant, psychomimetic properties [103]
 R = CH_3, C_6H_5, $(CH_2)_2OH$ n = 1, 2, 3	Antidepressants, antihistamines, anticholinergics [104]
 Z = $NHCH_3$, NH–n–C_4H_9, $N(CH_3)_2$, $N(C_2H_5)_2$	Tranquillizer [105]
 X–X = C–C, C–$(CH_2)_2$–C, C–O–C, C–S–C	No data [106]

[100] *D. A. Stauffer* and *O. E. Fancher*, J. org. Chemistry *25*, 935 (1960).

[101] U.S. Pat. 3048595, Smith, Kline & French Labs.

[102] Belg. Pat. 589043, Geigy AG.

[103] U.S. Pat. 3052721, Olin Mathieson Chem. Corp.

[104] Belg. Pat. 616905, N.V. Koninklijke Pharmaceutische V/H Brocades-Stheeman & 'Pharmacia.

[105] Belg. Pat. 610863, Ciba AG.

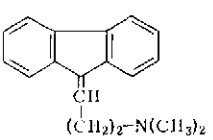
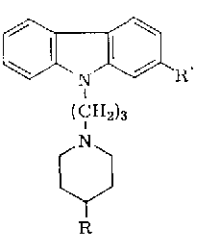
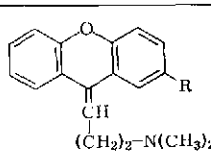
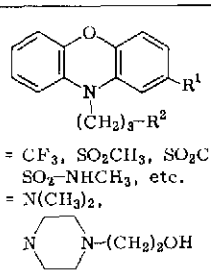
[106] *M. Thiel* and *K. Stach*, Mh. Chem. *93*, 1080 (1962).

the butyrophenone derivatives of the Haloperidol® type listed in Table 7. It appears as though a new type of activity has been found in this compound and current clinical investigations will give information on its usefulness in practice. A typical synthesis for FR 33 and analogous compounds is shown in Scheme 18.

5. Other Compounds

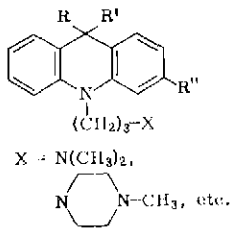
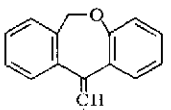
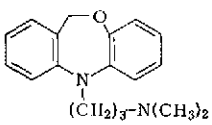
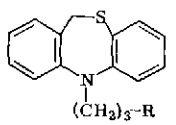
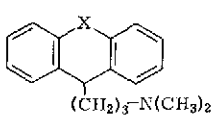
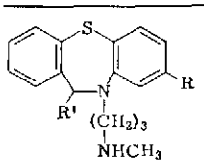
It is obvious from what has been said above that tricyclic psychotherapeutic agents have been investigated particularly intensively. Since we wish to limit ourselves to groups of substances which have led to drugs which are useful in practice or are at least undergoing clinical trial, we have indicated briefly in Tables 8 and 9 several structurally modified compounds, the practical aspects of which have not yet been evaluated. These are mentioned mainly because it is of interest to consider structures that differ from the "normal" basic side chains and the usual three-ring systems.

Table 9. Additional tricyclic systems investigated.

Compounds	Properties and References
	Compared with chlorpromazine, the neuroleptic activity is very weak [5]
 **R = H, OH, OCH_3, CH_2–CH_2OH etc.** **R' = H, $COCH_3$**	No data [107]
 R = CH_3, CF_3, OCH_3 SCH_3, Cl, $COCH_3$, etc. R = OCH_3 : Dimeprozan	Tranquilizers [108] Less active than chlorpromazine in psychotic patients [5]
	Tranquilizers, antiemetics [109]

[107] *K. Stach, M. Thiel*, and *F. Bickelhaupt*, Mh. Chem. *93*, 1090 (1962).

Table 9 (Continued)

Compounds	Properties and References
	Tranquilizers, reserpine antagonists, antiemetics [110]
	No data [42]
	Tranquilizer, antihistamine [111]
	Antidepressants [112]
	Activity similar to that of amitriptyline when tested for potentiation of narcosis, ataxia, inhibition of spontaneous mobility or of conditioned reflexes [113]
	Tranquilizers, antidepressants [114]

[108] Belg. Pat. 591847, Hoffmann-La Roche; French Pat. 1002 M Smith, Kline & French Labs.; compound with saturated side-chain: see also Belg. Pat. 600735, Smith, Kline & French Labs.

[109] Belg. Pat. 591069, Brit. Pat. 898073, Smith, Kline & French Labs.

[110] Brit. Pat. 857159, Smith, Kline & French Labs.; French Pat. 1279639, Geigy AG.; French Pat. 1364 M. Kefalas A/S.

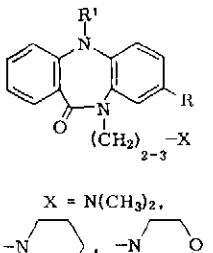
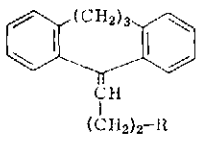
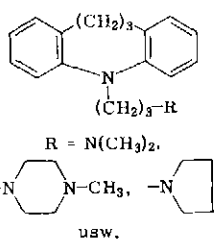
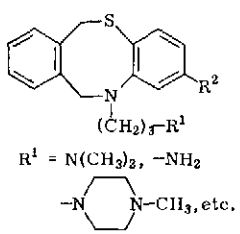
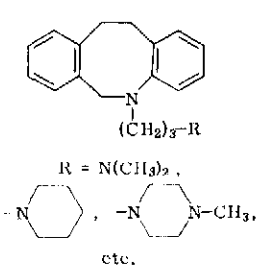
[111] U.S. Pat. 3069432, French Pat. 1317469, Olin Mathieson Chem. Corp.; see also U.S. Pat. 3071596.

[112] Belg. Pat. 617554, Société des usines chimiques Rhône-Poulenc.

[113] *S. O. Winthrop, M. A. Davis, F. Herr, J. Stewart*, and *R. Gaudy*, J. med. pharmac. Chem. *5*, 1199 (1962).

[114] Belg. Pat. 619890, Olin Mathieson Chem. Corp.; see also U.S. Pat. 3050524.

Table 9 (Continued)

Compounds	Properties and References
	No data [115] Tarpan® (Wander), antihistamine [116]
	No data [117] Central and peripheral effects similar to those of amitriptyline, but acting weaker centrally [117a].
	Antidepressants, sedatives, antiemetics, antihistamines, spasmolytics [118]
	Tranquilizers, antibistamines, spasmolytics [119]
	Antiallergics, anticholinergics, psycbotropic activity, analgesics [120]

[115] French Pat. 1295371, Dr. A. Wander AG.

[116] Belg. Pat. 611926, Parke, Davis & Co.

[117] *K. Stach* and *H. Spingler*, Mh. Chem. *93*, 889 (1962); *K. Stach* and *F. Bickelhaupt*, Mh. Chem. *93*, 896 (1962).

[117a] *S. O. Winthrop, M. A. Davis, F. Herr, J. Stewart* and *R. Gaudry*, J. med. Chem. *6*, 130 (1963).

[118] French Pat. 1339 M, Société des usines chimiques Rhône-Poulenc.

[119] U.S. Pat. 3079400, French Pat. 1317470, Olin Mathieson Chem. Corp.; see also U.S. Pat. 3079393.

[120] Belg. Pat. 616983, N.V. Koninklijke Pharmaceutische V/H Brocades-Stheeman & Pharmacia; see also Belg. Pat. 616984.

IV. Properties and Uses of Psychotherapeutic Agents

1. General

The etiology of psychic illness is multifactorial; contributing factors include physical, constitutional, and psychodynamic aspects, a trigger factor, and the social environment. Psychiatry deals with the relationships between man and the world he lives in, and psychotherapeutic drugs, combined with other measures, facilitate the attainment of these relationships. Figuratively, they have the function of opening the door for the physician to the psychic patient. Psychotherapeutic agents are not wonder drugs. They are also incapable of dealing with all the above factors. In contrast to the sedatives formerly used, *e.g.* barbiturates, the complex activity of modern psychotherapeutic agents transcends simple sedation, and, as a result of their central point of attack, they isolate psychic processes more or less specifically without appreciably influencing consciousness, as opposed to sleeping pills, for example. Many psychotherapeutic agents have a positive effect on psychoses, which were previously inaccessible to drug therapy.

The fact that different types of psychotherapeutic agents have a different type of action on the patient (psychosedative and pacifying or antidepressant and exhilarating) suggests that they have different mechanisms of activity and different points of attack on the central nervous system.

In descriptions of the activity of psychotherapeutic drugs, the term "antipsychotic effect" is frequently encountered. Since terms like "psychotic" and "schizophrenic" still cannot be satisfactorily comprehended and described, it is naturally impossible to define, describe, or reliably use the expression "antipsychotic". However, many psychiatrists are of the opinion that it is justifiable to apply the term "antipsychotic" to psychotropic drugs (phenothiazines, thioxanthenes, butyrophenone derivatives, benzoquinoline derivatives) which display not only direct short-term acute activity after administration, but also a more permanent activity that survives the actual action of the drug. These substances possess curative activity which is only partially or not at all associated with their sedative activity. We will show that some compounds which have strong sedative activity need not possess an antipsychotic effect; and contrarily, as will be shown below, tranquilizers, for example, are usually devoid of this effect.

Illnesses and symptoms which can be treated with modern psychotherapeutic agents are [121] schizophrenia, mania, and depression, organic psychoses, neurasthenic conditions, neuroses, and psychosomatic diseases, and also alcoholism and drug addiction. The diagnosis is associated with the following symptoms: acute serious excitability, states of anxiety and confusion, hallucination and delirium, insomnia, reduced general activity and vegetative disturbances.

[121] Cf. *F. Labhardt*, Schweiz. med. Wschr. *89*, 76, 105 (1959).

2. Properties and Use of Psychosedative Agents

a) Neuroleptics

Small doses of neuroleptics, especially those of the phenothiazine series, eliminate anxiety, uneasiness, and excitability in psychically healthy individuals; they are similar to the tranquilizers in this dosage range. Severe psychic disturbances can be treated with higher doses. Neuroleptics do not lead to a state of narcosis with diminished consciousness, as hypnotics for example do. The main effect of the neuroleptics is in the fields of schizophrenia, mania, and organic psychoses against anxiety, excitability, confusion, illusions, and hallucinations. In the phenothiazine series, thioridazine (Melleril® in Europe; Mellaril® in the U.S.A.) possesses both psychosedative and calmative activities and a very strong antidepressant action. Patients who suffered from fits of depression and who had attempted suicide were successfully treated with this compound. This example demonstrates the transition of the activity from the calmative to the antidepressant, exhilarating one.

It should be mentioned in passing that the *Rauwolfia* alkaloids, which chemically have nothing in common with phenothiazines, have the same principal effects.

b) Tranquilizers

Tranquilizers have pacifying effects equivalent to those already ascribed to sedatives. Their differentiation from the classical sedatives (barbiturates, alcohol) is not simple; the main difference being that, in therapeutic doses, the range between the sedative and hypnotic effects is greater in tranquilizers than in sedatives. In addition, tranquilizers produce special effects, for example, muscle relaxation (hence the term muscle relaxants). They are used for sedation in nonpathological circumstances, for example, in states of anxiety and tension. Here, there should be no interference with the ability to think and concentrate and with the general capabilities of the individual.

3. Properties and Uses of Antidepressants or Exhilarants

a) Thymoleptics

Although the most important representative of this series, imipramine (Tofranil®), is quite similar structurally to the phenothiazines, its main area of usefulness is in the treatment of depressive psychoses. Imipramine has an exhilarating, antipsychotic activity, which is particularly interesting in that it is not manifested in healthy subjects but only in pathologically depressed individuals. It is different in this respect from the pressor amines, which are known to exert their full stimulant activity even in the healthy individual. It can be shown that imipramine has not merely antidepressant activity since it has been used successfully to treat other psychotic symptoms, *e.g.* schizophrenic hallucinations.

b) Monoamine-oxidase Inhibitors

Compounds in this group have nothing in common chemically with the classical thymoleptics of the imipramine type, and their reaction mechanism is also different; however, according to their effect they belong to the same therapeutic class. Monoamine-oxidase inhibitors generally do not elevate the disposition (as do the pressor amines) but stimulate the drive. It is only secondarily that a change in disposition and possibly even euphoria may occur. In contrast to imipramine, compounds like Marsilide® also show stimulant activity in psychically normal, undepressed individuals. In general, monoamine-oxidase inhibitors are used in the same pathological circumstances as thymoleptics. A great deal is already known about the mechanism of action of these substances; the important factor in their mode of action is an increase in concentration of biogenic amines in the brain [122] caused by inhibition of the enzyme monoamine-oxidase.

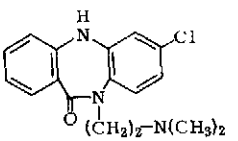
4. Properties and Uses of New Compounds with Psychotropic Activity

Modification of the phenothiazine tricyclic system, as described above, has led to numerous new compounds, some of which have characteristics of the classical neuroleptics, but some of which have thymoleptic and antidepressant properties. Thus, for example, thioxanthene neuroleptics have marked antidepressant activity. In this group of substances, the double bond connecting the basic side chain to the ring is important; hydrogenation of the double bond gives compounds without neuroleptic properties (Tremaril®, Wander).

A further modification of phenothiazine or thioxanthene consists in the introduction of a methylene group between a benzene ring and the sulfur atom; this yields the homophenothiazines and the homothioxanthenes. Little is known of the activity and practical applicability of the former, but extensive results have been obtained with the latter. It appears that the psychotropic activity of the homothioxanthenes is generally less than that of the thioxanthenes and is displaced even further in the antidepressant direction.

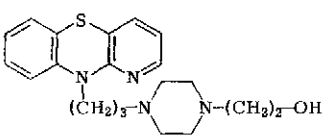
Recently, dibenzosuberone derivatives have aroused interest. Amitriptyline, the best known representative of this group, comes from the laboratories of Merck Sharp and Dohme in the U.S.A. This compound is described as an antidepressant with a marked psychosedative component feature. Many other dibenzocycloheptadiene derivatives have been prepared in our laboratory, and ID 22, described above, seems to have both psychotropic and intense antidepressant activities. If one compares the range of activity of many of the tricyclic psychopharmaceuticals derived from phenothiazine, it becomes apparent that the basic characteristic is the same; either the psychosedative or the antidepressant properties predominate. Apparently, the ring system alone is not strongly specific for the occurrence of these two kinds of activity; its nature produces only slight qualitative and even quantitative differences rather than fundamental differences in activity.

Psychotropic properties were discovered ten years ago incidentally in phenothiazine derivatives used primarily as antihistamines. Since then, extensive development in this area of research has led to the synthesis and testing of thousands of new compounds with the result that a whole spectrum of psychotropic agents is available to the physician today. This applied research work has yielded not only compounds useful in psychiatry but also materials with other activities and valuable therapeutic properties. We have mentioned that modification of the typical basic side chain of the tricyclic compounds to give compounds of the cyproheptadine type (BP 400 and AP 800) has led to especially active antihistamines and serotonin inhibitors. Modification of the tricycle and shortening of the basic side chain yielded the antihistamine Tarpan®.

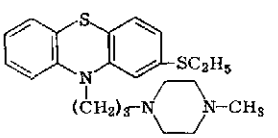


Tarpan®

By changing the basic side chain and the tricyclic system of the classical neuroleptics of the phenothiazine series, it became possible to obtain compounds in which the antiemetic components dominated the psychosedative properties. As examples, the commercial products Pervetral® and Torecan® are shown. In this connection,

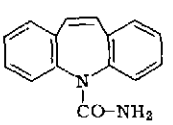


Pervetral® (Homburg)



Torecan® (Sandoz)

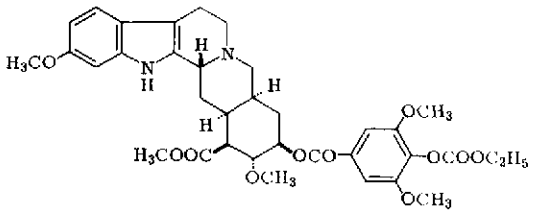
an interesting compound (G 32883) with anticonvulsant properties was prepared in the laboratories of J. R. Geigy A.G., Basel.



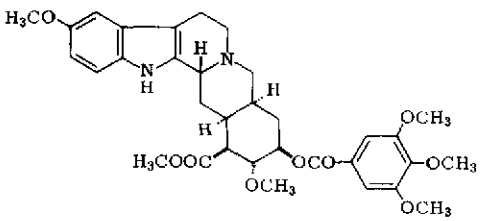
G 32 883 (Geigy)

Partial and total synthesis of reserpine analogues led to compounds which have practically no psychotropic activity but which have valuable hypotensive activities, *e.g.* Singoserp® and methoserpidine.

[122] *A. Pletscher, K. F. Gey,* and *P. Zeller,* Monoaminoxydase-Hemmer, in *E. Jucker:* Fortschritte der Arzneimittelforschung. Birkhäuser, Basel and Stuttgart 1960, Vol. 2, p. 417.

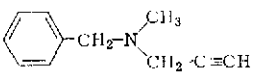


Singoserp® (CIBA)



Methoserpidine (SANDOZ, ROUSSEL)

Several compounds with different types of activities were also obtained from the monoamine-oxidase inhibitor series; they play a role in the treatment of angina pectoris and as a blood pressure-lowering drug (Pargyline). Recent work has also indicated that this direction of chemical research may even touch upon the important field of cytostatic drugs.



Pargyline
Eutonyl® (ABBOTT)

Even though it has become possible to create drugs which open up areas of psychiatry that were hitherto inaccessible to treatment, we are still far away from the ideal drugs which will effect lasting cures of these ailments. Although some of these compounds show antipsychotic activity which outlasts the treatment, their whole effect does not go far beyond palliative therapy. Only when we have a clear understanding of the etiology and nature of psychic disturbances will it be possible to strike at the root of these diseases, which are today among the most widespread of medical disorders.

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Recent Developments in the Chemistry of Metal Silyls of the Type $M(SiR_3)_n$

BY PROF. DR. E. WIBERG, DR. O. STECHER, DR. H. J. ANDRASCHECK [1], DR. L. KREUZBICHLER [2], AND DR. E. STAUDE [3]

INSTITUT FÜR ANORGANISCHE CHEMIE DER UNIVERSITÄT MÜNCHEN (GERMANY)

Dedicated to Dr. W. Foerst on the occasion of his 65th birthday

Whereas rapid strides have recently been made in the chemistry of the silyls of nonmetals, our knowledge of metal silyls is still scanty. Silyl compounds with every nonmetal are now known, but the literature on metal silyls is almost entirely restricted to silyl compounds of the alkali metals. This is all the more surprising, since the closely related field of elemental-homologous organometallic compounds of the type $M(CR_3)_n$ (where M = metal, R = hydrogen and/or organic residue, and n = valence of the metal) is among the most interesting and extensively studied areas of chemistry. This report will therefore deal with the results of recent investigations on metal silyls which led beyond the alkali silyls to silyl compounds of the alkaline earth metals, zinc, mercury, aluminum, and tin.

A. Group I of the Periodic Table

Preparation of Alkali Metal Triphenylsilyls $MSiPh_3$ in Liquid Ammonia [*]

In 1951, *Gilman* [4] reported the preparation of triphenylsilylpotassium $KSiPh_3$ by cleavage of hexaphenyldisilane $Ph_3Si-SiPh_3$ with potassium metal (in the form of a Na–K alloy) in ether. The yellowish-brown compound was obtained as a suspension in ether. The triphenylsilyl compounds of rubidium and cesium were obtained analogously, but sodium and lithium did not cleave $(SiPh_3)_2$ in ether. Further study of this

[1] *H. J. Andrascheck:* „Zur Kenntnis von Alkalimetallsilylen $MSiPh_3$", Diploma Thesis, Universität München, 1962; „Zur Kenntnis neuer Metallsilyle", Ph. D. Thesis, Universität München, 1962.

[2] *L. Kreuzbichler:* „Über Darstellung und Eigenschaften des Trimethylsilyljodids $(CH_3)_3SiJ$", Diploma Thesis, Universität München, 1959; „Zur Frage der Existenz von Aluminiumsilylen", Ph. D. Thesis, Universität München, 1961.

[3] *E. Staude:* „Bis-trimethylsilyl-quecksilber, eine erste Verbindung mit direkter Silicium-Quecksilber-Bindung", Diploma Thesis, Universität München, 1959; „Si–Si-Synthesen über Si–Hg-Verbindungen", Ph. D. Thesis, Universität München, 1960.

[*] Experimental work carried out by *H. J. Andrascheck* [1]; Ph = C_6H_5.

[4] *H. Gilman* and *T. C. Wu*, J. Amer. chem. Soc. 73, 4031 (1951).

reaction resulted in the expected conclusion that the cleavage is strongly dependent upon the solvent. Thus, for example, in ethylene glycol dimethyl ether, $(SiPh_3)_2$ is cleaved by sodium and lithium, yielding solutions of the silyls $LiSiPh_3$ and $NaSiPh_3$. These, however, are not very stable (ether cleavage) and must therefore be used immediately after preparation. Solutions obtained by cleaving $(SiPh_3)_2$ with alkali metals in tetrahydrofuran are less labile.

Since alkali metals are readily soluble in liquid ammonia, it seemed reasonable to include this solvent in our investigations, particularly since only vague indications as to its use were found in the literature.

It was established that $(SiPh_3)_2$ is readily cleaved by Li, Na, or K in liquid ammonia:

$$2\ M^{I} + Ph_3Si{-}SiPh_3 \rightarrow 2\ M(SiPh_3) \qquad (1)$$

The rate of reaction increases from lithium to potassium, *e.g.* after 4 hours at -50 °C, the conversion with lithium was 60 %, with sodium 70 %, and with potassium quantitative. The metal silyls $MSiPh_3$ produced remain dissolved in the liquid ammonia. The color darkens progressively in the series $LiSiPh_3$ (yellow), $NaSiPh_3$ (orange), $KSiPh_3$ (red-brown).

Stability to ammonolysis is rather high and increases in the direction $LiSiPh_3 \rightarrow NaSiPh_3 \rightarrow KSiPh_3$, as shown by the reaction with n-butyl chloride BuCl:

$$BuCl + MSiPh_3 \rightarrow BuSiPh_3 + MCl \qquad (2)$$

Reaction *(2)* gave high yields of triphenylsilylbutane $BuSiPh_3$ even after the $MSiPh_3$ solutions had been left standing for hours; in the case of the potassium compound the yield was quantitative.

Attempts to isolate the alkali metal silyls $MSiPh_3$ by evaporation of the ammonia were successful only in the case of the potassium compound, which separated as an undecomposed, golden-yellow solid. On the other hand, the solid, yellow silyls $LiSiPh_3$ and $NaSiPh_3$ decomposed while being worked up. This decomposition consisted partly of a disproportionation according to the reaction

$$2\ MSiPh_3 \rightarrow 2\ M + SiPh_4 + SiPh_2 \qquad (3)$$

liberating the metal and forming tetraphenylsilane $SiPh_4$ and polymeric phenylsilanes $Ph_3{-}(SiPh_2)_n{-}SiPh_3$ (cf. Section C.I), and partly of a solvolysis by ammonia yielding the metal amide and hexaphenyldisilazane, with evolution of hydrogen, according to equation *(4)*.

$$2\ MSiPh_3 + 3\ NH_3 \rightarrow 2\ MNH_2 + 2\ H_2 + HN(SiPh_3)_2 \qquad (4)$$

The stable solutions of triphenylsilylpotassium obtained by treatment of $(SiPh_3)_2$ with K in liquid ammonia are, therefore, singularly well suited for use in further reactions. We have especially investigated the metathesis of $KSiPh_3$ with metal chlorides since it was expected that this reaction would yield new metal silyls of the type $M(SiPh_3)_n$ according to *(5)*.

$$MCl_n + n\ KSiPh_3 \rightarrow M(SiPh_3)_n + n\ KCl \qquad (5)$$

More will be said on this subject in Sections B. II, B. V., and C. II.

B. Group II of the Periodic Table

I. Alkaline Earth Metal Triphenylsilyls $M(SiPh_3)_2$ [*]

The alkaline earth metals Ca, Sr, and Ba do not react with hexaphenyldisilane $(SiPh_3)_2$ in suspension in tetrahydrofuran even after standing for several days. However, when dissolved in liquid ammonia, they do cleave the Si–Si bond in a reaction similar to that formulated in *(1)*.

$$M^{II} + Ph_3Si{-}SiPh_3 \rightarrow (Ph_3Si)M(SiPh_3) \qquad (6)$$

The products are the hitherto unknown alkaline earth silyls $M(SiPh_3)_2$. The rate of the cleavage reaction and the resistance of the products to solvolysis follow the trend observed in the alkali metal compounds (Section A). Thus, both phenomena increase with rising atomic number of the metal (*i.e.* with increasing salt character of the silyl compounds) in the direction Ca → Sr → Ba. However, the rate of formation and resistance to solvolysis of individual alkaline earth metal silyls are considerably lower than those of the corresponding alkali metal compounds of the preceding group. $Ca(SiPh_3)_2$ and $Sr(SiPh_3)_2$ are formed so slowly and ammonolyse so readily that, even after a reaction time of several hours, the major part (80–90 %) of the starting material $(SiPh_3)_2$ is recovered unchanged, and the small quantities of $Ca(SiPh_3)_2$ and $Sr(SiPh_3)_2$ formed are completely solvolysed while the product is being worked up and cannot be isolated.

On the other hand, $Ba(SiPh_3)_2$ resists ammonolysis if the temperature is not allowed to rise too high, and it can be isolated in very good yield from the liquid ammonia. It is an orange-yellow substance, insoluble in benzene but soluble in tetrahydrofuran with a golden-yellow color. It reduces silver nitrate to Ag and is hydrolysed in aqueous methanol to triphenylsilanol, evolving hydrogen:

$$Ba(SiPh_3)_2 + 4\ H_2O \rightarrow Ba(OH)_2 + 2\ H_2 + 2\ SiPh_3OH \qquad (7)$$

When heated to 160 °C, the compound blackens and decomposes with the formation of polyphenylsilanes (*e.g.* decaphenyltetrasilane, Si_4Ph_{10}), cf. Section C.I.

The ammonolysis according to *(8)* is analogous to the

$$Ba(SiPh_3)_2 + 4\ NH_3 \rightarrow Ba(NH_2)_2 + 2\ H_2 + 2\ SiPh_3NH_2 \qquad (8)$$

hydrolysis in *(7)* with the evolution of hydrogen and the formation of triphenylsilylamine $SiPh_3NH_2$ and barium amide $Ba(NH_2)_2$. These products interact further:

$$Ba(NH_2)_2 + 2\ H_2NSiPh_3 \rightarrow Ba(HNSiPh_3)_2 + 2\ NH_3 \qquad (9)$$

to give barium triphenylsilylamide $Ba(HNSiPh_3)_2$. This colorless product is extremely reactive in air, in which it is apt to explode and ignite; it hydrolyses in moist methanol to give triphenylsilylamine $SiPh_3NH_2$ and triphenylsilanol.

$$Ba(HNSiPh_3)_2 + 2\ H_2O \rightarrow Ba(OH)_2 + 2\ SiPh_3NH_2 \qquad (10)$$

It forms ammoniates with ammonia and, in contrast to $Ba(SiPh_3)_2$, does not reduce $AgNO_3$ to metallic silver.

[*] Experimental work by *H. J. Andrascheck* [1]; Ph = C_6H_5.

II. Bis(triphenylsilyl)zinc $Zn(SiPh_3)_2$ [*]

The reaction between $ZnCl_2$ and $KSiPh_3$ was studied as an example of the preparation of new metal silyls of the type $M(SiPh_3)_n$ by metathesis of metal chlorides MCl_n with triphenylsilylpotassium $KSiPh_3$ in liquid ammonia according to *(5)*.

If a solution of $KSiPh_3$ in liquid ammonia is prepared according to

$$2\,K + (SiPh_3)_2 \rightarrow 2\,KSiPh_3$$

and anhydrous $ZnCl_2$ (mole ratio of $ZnCl_2$:$KSiPh_3$ = 1:2) is added in portions with careful exclusion of air and moisture, an exothermic reaction results with the disappearance of the red-brown color of the $KSiPh_3$ solution and the formation of a pale yellow precipitate. The ammonia is allowed to evaporate and the $Zn(SiPh_3)_2$ formed can be extracted with dry benzene in which it is soluble, leaving an insoluble residue of KCl. The benzene is removed by distillation, and the $Zn(SiPh_3)_2$ is obtained as an ivory-colored powder. The yield is 85 %, based on $(SiPh_3)_2$. The reaction may be described by the equation

$$ZnCl_2 + 2\,KSiPh_3 \rightarrow Zn(SiPh_3)_2 + 2\,KCl \qquad (11)$$

Bis(triphenylsilyl)zinc, the first compound containing a Zn–Si bond to be isolated, is monomeric in benzene solution (molecular-weight determination by cryoscopy), forms ammoniates with ammonia, reduces $AgNO_3$ to Ag, and is readily hydrolysed by acids and bases. The reaction with dilute hydrochloric acid proceeds according to *(12)*

$$Zn(SiPh_3)_2 + 2\,H_2O \xrightarrow{H^+} Zn(OH)_2 + 2\,SiPh_3H \qquad (12)$$

and forms triphenylsilane without evolution of hydrogen. The triphenylsilane $SiPh_3H$ is converted into triphenylsilanol $SiPh_3OH$ or its anhydride $(SiPh_3)_2O$ by treatment with ethanolic KOH, with evolution of hydrogen [2 moles of H_2 per mole of $Zn(SiPh_3)_2$]:

$$Zn(SiPh_3)_2 + 4\,H_2O \xrightarrow{OH^-} Zn(OH)_2 + 2\,SiPh_3OH + 2\,H_2 \qquad (13)$$

On heating above 105 °C, $Zn(SiPh_3)_2$ decomposes with separation of metallic zinc. However, contrary to expectation, the reaction does not take place according to *(14)*, *i.e.* no hexaphenyldisilane is formed along with the free metal.

$$Zn(SiPh_3)_2 \not\rightarrow Zn + (SiPh_3)_2 \qquad (14)$$

Instead, a mixture of tetraphenylsilane $SiPh_4$ and of higher polyphenylsilanes Si_nPh_{2n+2} is obtained. Just like the barium compound $Ba(SiPh_3)_2$, the $Zn(SiPh_3)_2$ apparently disproportionates on heating according to *(15)*.

$$Zn(SiPh_3)_2 \rightarrow Zn + SiPh_4 + SiPh_2 \qquad (15)$$

The products are tetraphenylsilane and diphenylsilene, the latter polymerizing to polyphenylsilanes with $SiPh_3$ end groups, $Ph_3Si-(SiPh_2)_n-SiPh_3$ (cf. Section C.I).

[*] Experimental work by *H. J. Andrascheck* [1].

III. Bis(trimethylsilyl)mercury $Hg(SiMe_3)_2$ [*]

While studying the applicability of the Wurtz reaction to the synthesis of organosubstituted disilanes, an attempt was made to prepare hexamethyldisilane Si_2Me_6 by treatment of trimethylhalogenosilanes Me_3SiX (X = Cl, Br, or I) with liquid sodium amalgam according to the reaction:

$$Me_3SiX + 2\,Na + XSiMe_3 \rightarrow Me_3Si-SiMe_3 + 2\,NaX \qquad (16)$$

However, the products obtained at room temperature were not those expected from *(16)*. Instead, mercury was found to have been incorporated into the product to yield exclusively bis(trimethylsilyl)mercury $Hg(SiMe_3)_2$:

$$Me_3SiX + 2\,Na + Hg + XSiMe_3 \rightarrow Me_3Si-Hg-SiMe_3 + 2\,NaX \qquad (17)$$

The compound $Hg(SiMe_3)_2$, which is easily prepared by shaking liquid Me_3SiBr with Na/Hg for several days, forms beautiful, highly refractive, yellow crystals, which sublime undecomposed *in vacuo* at 60 °C and melt with decomposition at 102–104 °C. At 70 °C (start of decomposition), the solid has a vapor pressure of approximately 1 mm. It is soluble in ether, tetrahydrofuran, benzene, n-hexane, and carbon disulfide, as well as in its starting material Me_3SiX and in the product of its decomposition, Si_2Me_6 (see below). The molecular weight in ether solution corresponds to the monomeric formula $Hg(SiMe_3)_2$. A strong absorption peak, attributable to the Hg–Si bonds, appears at 318 cm^{-1} in the CsBr region of the infrared spectrum. Contrary to the behavior of dimethylmercury, $Hg(SiMe_3)_2$ does not react with zinc at elevated temperatures in an exchange reaction to give the zinc silyl $Zn(SiMe_3)_2$.

On heating at 100–160 °C for several days, $Hg(SiMe_3)_2$ is quantitatively decomposed to hexamethyldisilane and mercury (mole ratio 1:1).

$$Me_3Si-Hg-SiMe_3 \rightarrow Me_3Si-SiMe_3 + Hg \qquad (18)$$

Reaction *(18)* can be used for the analysis of the compound, since quantitative determination of the only reaction products, $(SiMe_3)_2$ and Hg, is simple. Light accelerates the decomposition, which in ether solution is complete after a few days' standing even at room temperature.

When *(17)* and *(18)* are combined, the equation for the overall reaction represents the Wurtz synthesis originally intended *(16)*. Thus, when sodium amalgam is used as halogen acceptor, the Wurtz synthesis proceeds via an intermediate mercury compound that can be isolated at room temperature.

In the reaction of trimethylsilylmercury with hydrogen chloride

$$Me_3Si-Hg-SiMe_3 + HCl \rightarrow Me_3SiH + Hg + ClSiMe_3 \qquad (19)$$

mercury is liberated and equimolar quantities of trimethylsilane Me_3SiH and trimethylchlorosilane Me_3SiCl are formed; *(19)* may thus also be used for analysis of the compound.

[*] Experimental work by *E. Staude* [3]; Me = CH_3.

Bis(trimethylsilyl)mercury $Hg(SiMe_3)_2$ constitutes an interesting addition to the class of metal silyls $M(SiR_3)_n$, for it is not only the first compound containing an Hg–Si bond which has been isolated, but also the first example of a volatile (suhlimable) metal silyl. It is more stable than the corresponding carbon compound $Hg(CMe_3)_2$, which decomposes and liberates mercury at 40 °C.

IV. Formation and Decomposition of Methylated Mercury Silyls $Hg(SiMe_{3-n}H_n)_2$ [*]

As described in section B.III, the reaction of trimethylbromosilane Me_3SiBr with liquid sodium amalgam Na/Hg *(20)* at room temperature leads to the formation of bis(trimethylsilyl)mercury $Hg(SiMe_3)_2$, which can be separated from the by-product NaBr by sublimation *in vacuo* at 60 °C and which decomposes above 70 °C to form mercury and hexamethyldisilane Si_2Me_6 according to *(21)*:

$$Hg + 2\,Na + 2\,BrSiMe_3 \rightarrow 2\,NaBr + Hg(SiMe_3)_2 \qquad (20)$$

$$Hg(SiMe_3)_2 \rightarrow Hg + (SiMe_3)_2 \qquad (21)$$

On the other hand, *Stock* and *Somieski* [5] report that no intermediate disilylmercury $Hg(SiH_3)_2$ can be detected in the analogous reaction of the parent substance H_3SiCl with Na/Hg. The end product of the reaction *(22)* is not disilane $(SiH_3)_2$ but its disproportionation products SiH_4 and $(SiH_2)_x$ as in *(23)*; the $(SiH_2)_x$ then partly disproportionates into SiH_4 and $(SiH)_x$.

$$Hg + 2\,Na + 2\,ClSiH_3 \rightarrow 2\,NaCl + Hg(SiH_3)_2 \qquad (22)$$

$$Hg(SiH_3)_2 \rightarrow Hg + SiH_2 + SiH_4 \qquad (23)$$

There was, therefore, some interest in examining the possibility of isolation and the decomposition behavior of the two partially methylated mercury silyls $Hg(SiMe_2H)_2$ and $Hg(SiMeH_2)_2$, which are intermediates between $Hg(SiMe_3)_2$ and $Hg(SiH_3)_2$. This study required the prior synthesis and further treatment with sodium amalgam of the two hitherto unknown bromosilanes Me_2HSiBr and MeH_2SiBr. These were prepared from Me_2SiH_2 and $MeSiH_3$, respectively, by partial bromination with HBr at room temperature, using $AlBr_3$ as catalyst. The reaction with Na/Hg gave the following results.

1. Reaction of Na/Hg with Me_2HSiBr

When shaken for a few days at room temperature with liquid sodium amalgam, liquid dimethylbromosilane Me_2HSiBr [6] yields bis(dimethylsilyl)mercury according to *(24)*

$$Hg + 2\,Na + 2\,BrSiMe_2H \rightarrow 2\,NaBr + Hg(SiMe_2H)_2 \qquad (24)$$

However, the $Hg(SiMe_2H)_2$ cannot be isolated since it is so unstable that it decomposes during the reaction. As a painstaking investigation revealed, the decomposition proceeds via two different paths:

a) A minor part (approximately 20 %) of the $Hg(SiMe_2H)_2$ decomposes via *(25)*, which is analogous to *(21)*.

$$Hg(SiMe_2H)_2 \rightarrow Hg + (SiMe_2H)_2 \qquad (25)$$

This yields the previously unknown compound tetramethyldisilane $Si_2Me_4H_2$ (a colorless liquid, monomeric in the vapor phase; m.p. 92 °C, b.p. 88 °C; vapor pressure at 0 °C: 21.8 mm) along with the liberation of Hg.

b) The major proportion (approximately 80 %) reacts via *(26)*

$$Hg(SiMe_2H)_2 \rightarrow HgSiMe_2 + SiMe_2H_2 \qquad (26)$$

by elimination of dimethylsilane $SiMe_2H_2$ to form dimethylsilylene mercury $HgSiMe_2$ [7], part of which decomposes to Hg + $SiMe_2$ [cf. *(23)*] and part of which forms a polymer $(HgSiMe_2)_n$.

As will be described later (Section C.I), the dimethylsilene $SiMe_2$ becomes saturated by acquiring $SiMe_2H$ end groups from $Hg(SiMe_2H)_2$, forming hexamethyltrisilane $HMe_2Si–SiMe_2\ SiMe_2H$ (a colorless liquid with monomeric vapor; m.p −68 °C; vapor pressure at 0 °C: 2.2 mm), octamethyltetrasilane $HMe_2Si–(SiMe_2)_2–SiMe_2H$ (colorless crystals, monomeric in the vapor phase, with no measurable vapor pressure at 0 °C), and decamethylpentasilane, $HMe_2Si–(SiMe_2)_3–SiMe_2H$ (nonvolatile). All these compounds, as well as the first member of the series, $HMe_2Si–SiMe_2$, were hitherto unknown.

The polymeric mercury silylene $(HgSiMe_2)_n$, which may also be prepared from Na/Hg and Br_2SiMe_2, can be extracted with hexane, benzene, or ether from the residue remaining after all the volatile reaction products have been distilled off. Removal of the solvent from the yellow extract leaves an orange-yellow, very viscous oil, which is decomposed by light or by heating above 60 °C *(27)*, liberating mercury.

$$(HgSiMe_2)_n \rightarrow n\,Hg + (SiMe_2)_n \qquad (27)$$

The decomposition product, polymeric dimethylsilene $(SiMe_2)_n$, is a waxy, colorless, nonvolatile mass, soluble in hexane, benzene, and ether [8].

The following material balance, obtained in a reaction between HMe_2SiBr and Na/Hg, will serve as an illustration of the mole ratios involved in these processes (the numbers are millimoles).

$$7.18\ HMe_2SiBr + 7.18\ Na \rightarrow$$
$$7.18\ NaBr + 2.82\ SiMe_2H_2 + 0.60\ Si_2Me_4H_2 + 0.05\ Si_3Me_6H_2$$
$$+ 0.08\ Si_4Me_8H_2 + 0.04\ Si_5Me_{10}H_2 + 2.49\ (SiMe_2)_n$$

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[*] Experimental work by *E. Staude* [3]; Me = CH_3.

[5] *A. Stock* and *C. Somieski*, Ber. dtsch. chem. Ges. *54*, 524 (1921).

[6] Me_2HSiBr: colorless, mobile liquid, fumes in air, monomeric in the vapor phase, density at 0 °C: 1.35 g/cm³; m.p. −84 °C, b.p. 57.7 °C, log p = −1640.6/T + 7.8383.

[7] To some extent, reaction *(26)* may be regarded as the disproportionation of a "primary mercury salt" $Hg(HSiMe_2)_2$ into a "secondary mercury salt" $HgSiMe_2$ and a "free acid" H_2SiMe_2. Such disproportionations are also known to occur in organic chemistry with metal alkyls.

[8] The mass begins to melt at 60 °C, to evaporate slightly at 90 °C *in vacuo* and forms a clear, transparent melt at 105 °C. In addition to dimethyldibromosilane $SiMe_2Br_2$, its bromination also produces the hitherto unknown tetramethyldibromodisilane $Si_2Me_4Br_2$ (colorless crystals; sublimes *in vacuo* at room temperature; monomeric vapor; m.p. 58 °C).

2. Reaction of Na/Hg with MeH_2SiBr

Also in the reaction of monomethylbromosilane $H_2MeSiBr$ with Na/Hg [9], the bis(methylsilyl)mercury $Hg(SiMeH_2)_2$ expected as primary product of the reaction *(28)* by analogy to *(20)*

$$Hg + 2\,Na + 2\,BrSiMeH_2 \rightarrow 2\,NaBr + Hg(SiMeH_2)_2 \qquad (28)$$

cannot be isolated because of its extreme instability and consequent immediate decomposition. The volatile portion of the decomposition product does not contain dimethyldisilane $(SiMeH_2)_2$. The decomposition reaction is therefore not analogous to *(25)*. By analogy to *(26)*, one would expect to find Hg(SiMeH) and $SiMeH_3$ by *(29)*.

$$Hg(SiMeH_2)_2 \rightarrow Hg(SiMeH) + SiMeH_3 \qquad (29)$$

Monomethylsilane $MeSiH_3$ was indeed found to be the major constituent of the volatile fraction of the product. It was present in a ratio of 0.5 mole of $MeSiH_3$ per mole of $MeSiH_2Br$, *i.e.* in a quantity corresponding to the sum of *(28)* and *(29)*. However, instead of silylenemercury Hg(SiMeH), the reaction mixture contained the decomposition product $(SiMeH)_n$ in analogy to *(27)*. The degree of polymerization apparently varied since the polymer consisted in part of a colorless, volatile liquid, in part of a nonvolatile oil soluble in hexane, and in part of a nonvolatile solid insoluble in hexane [10].

The material balance of the reaction between Na/Hg and $H_2MeSiBr$ is illustrated by the following example (numerical values in millimoles):

$$10.8\,H_2MeSiBr + 10.8\,Na \rightarrow 10.8\,NaBr + 5.4\,MeSiH_3 + 5.4\,(MeSiH)_n$$

The course of the reaction is therefore similar to that of Na/Hg with H_3SiCl [*(22)* and *(23)*].

Taking into account the discussion in Section B.III, we may conclude that the primary products of the reaction between sodium amalgam Na/Hg and the silyl bromides $Me_nH_{3-n}SiBr$ are the methylated mercury silyls $Hg(SiMe_nH_{3-n})_2$, where n = 1, 2, or 3, which decompose via two different routes: (a) with formation of methylated disilanes $(SiMe_nH_{3-n})_2$, and (b) with formation of the disproportionation products of the former, $SiMe_nH_{4-n}$ and $SiMe_nH_{2-n}$. The first pathway is favored by a greater, the second by a lesser methyl content. Thus, the compound richest in methyl groups, *viz.* $Hg(SiMe_3)_2$, yields exclusively $(SiMe_3)_2$, while that with the fewest, *viz.* $Hg(SiMeH_2)_2$, gives only $SiMeH_3$ + SiMeH. Decomposition of the intermediate compound $Hg(SiMe_2H)_2$ proceeds via both routes. The mercury compounds which are the precursors of the reaction products are unstable and only the permethylated species can be isolated, *i.e.* $Hg(SiMe_3)_2$ in case (a) and $HgSiMe_2$ in case (b).

[9] $H_2MeSiBr$: mobile, colorless liquid, fumes in air, vapor monomeric, b.p. 32 °C, log p = −1486.6/T + 7.7200; cf. *E. A.V. Ebsworth* and *H. J. Emeléus*, J. chem. Soc. (London) *1958*, 2150.

[10] In addition to hydrogen bromide, bromination of $(SiMeH)_n$ yields the hitherto unknown compound dimethyltetrabromodisilane $Si_2Me_2Br_4$ (colorless crystals; sublimes *in vacuo* at room temperature; vapor monomeric; m.p. 93 °C). This compound and the $Si_2Me_4Br_2$ mentioned in [8] close the gap in the disilane series $(SiMe_nBr_{3-n})_2$, so that all four members of this series (n = 0, 1, 2, or 3) are now known.

V. Preparation of Bis(triphenylsilyl)mercury $Hg(SiPh_3)_2$ [*]

Like zinc chloride $ZnCl_2$ (Section B.II), mercuric chloride $HgCl_2$ reacts with triphenylsilylpotassium $KSiPh_3$ in liquid ammonia according to *(30)*.

$$HgCl_2 \xrightarrow[-KCl]{+\,KSiPh_3} Hg(SiPh_3)Cl \xrightarrow[KCl]{+\,KSiPh_3} Hg(SiPh_3)_2 \qquad (30)$$

The products of this reaction are the unstable mercury silyls $Hg(SiPh_3)Cl$ and $Hg(SiPh_3)_2$, which are largely decomposed according to *(31)* and *(32)* while still in the reaction mixture. Thus, the major products obtained

$$Hg(SiPh_3)Cl \rightarrow Hg + SiPh_3Cl \quad \left(\xrightarrow{+\,NH_3} SiPh_3NH_2\right) \qquad (31)$$

$$Hg(SiPh_3)_2 \rightarrow Hg + (SiPh_3)_2 \qquad (32)$$

are triphenylsilylamine $SiPh_3NH_2$ and hexaphenyldisilane $(SiPh_3)_2$ [11]. Small quantitites of undecomposed yellow bis(triphenylsilyl)mercury $Hg(SiPh_3)_2$ can also be identified. This compound is soluble in benzene and is sensitive to air and light. Because of its low decomposition temperature (55–60 °C), it is difficult to separate from the co-product triphenylsilylamine $SiPh_3NH_2$; besides, the solubilities of the two compounds are similar. For example, both $SiPh_3NH_2$ and $Hg(SiPh_3)_2$ are soluble in benzene, whereas $(SiPh_3)_2$ is not. Benzene can therefore be used to separate $Hg(SiPh_3)_2$ from KCl, Hg, and $(SiPh_3)_2$, but not from triphenylsilylamine.

C. Group III of the Periodic Table

I. The Question of the Existence of Tris(trimethylsilyl)aluminum $Al(SiMe_3)_3$ [**]

When it was discovered (see Section B.III) that bistrimethylsilylmercury could be successfully prepared from Na/Hg and trimethylsilyl halides Me_3SiX, it appeared feasible to use $Hg(SiMe_3)_2$ as a starting material in the synthesis of additional metal silyls, particularly of tris(trimethylsilyl)aluminum $Al(SiMe_3)_3$. The latter compound was of special interest in view of the use of trialkylaluminum compounds in the polymerization of ethylene. Thus, $Hg(SiMe_3)_2$ was treated with either Al or with $\rangle$Al–H. In both cases it was found that the $\rangle$Al–$SiMe_3$ group is unstable and is spontaneously converted into $\rangle$Al–Me, with elimination of $SiMe_2$ according to *(33)*.

$$\rangle AlSiMe_3 \rightarrow \rangle Al{-}Me + SiMe_2 \qquad (33)$$

This decomposition illustrates the essential difference between the chemistries of carbon and of silicon. By analogy to the

[*] Experimental work by *H. J. Andrascheck* [1]; Ph = C_6H_5.

[11] The presence of small amounts of tetraphenylsilane $SiPh_4$ among the decomposition products shows that a small amount of the bis(triphenylsilyl)mercury $Hg(SiPh_3)_2$ may decompose by the reaction

$$Hg(SiPh_3)_2 \rightarrow Hg + SiPh_4 + SiPh_2$$

instead of by reaction *(32)*. This behavior is analogous to that of the methylated mercury silyls (Section B.IV).

[**] Experimental work by *L. Kreuzbichler* [2]; Me = CH_3.

behavior of similar organometallic compounds, decomposition of the silyl compound $Al(SiMe_3)_3$ might have been expected to yield $AlH(SiMe_3)_2$, $AlH_2(SiMe_3)$, and AlH_3, together with "silica-isobutene" $CH_2{=}SiMe_2$, or "poly-(silica-isobutene)" $(-CH_2-SiMe_2-)_x$ since the isologous organometallic compounds, such as the t-butyl compounds, tend to form metal hydrides by splitting off isobutene.

1. Reaction of $Hg(SiMe_3)_2$ with Al

When dimethylmercury $Hg(CH_3)_2$ is treated with activated aluminum, the mercury is exchanged for Al according to *(34)*.

$$3\ Hg(CH_3)_2 + 2\ Al \rightarrow 3\ Hg + 2\ Al(CH_3)_3 \qquad (34)$$

The reaction proceeds (although slowly) even at room temperature, but is more rapid at 80 °C [12]. Expecting to obtain the desired tris(trimethylsilyl)aluminum $Al(SiMe_3)_3$ in a reaction *(35)* analogous to *(34)*

$$3\ Hg(SiMe_3)_2 + 2\ Al \rightarrow 3\ Hg + 2\ Al(SiMe_3)_3 \qquad (35)$$

we treated bis(trimethylsilyl)mercury with excess activated aluminum. A slow reaction between $Hg(SiMe_3)_2$ and Al begins at 60 °C. However, to achieve a sufficiently rapid conversion (1 to 3 days), the temperature must be raised to 80 °C. At that temperature, partial decomposition of $Hg(SiMe_3)_2$ according to *(36)* (which starts at 70 °C – cf. Section B.III) cannot be avoided.

$$Hg(SiMe_3)_2 \rightarrow Hg + (SiMe_3)_2 \qquad (36)$$

Reaction *(35)* resulted in quantitative consumption of $Hg(SiMe_3)_2$ and liberation of metallic Hg. The product was a colorless liquid which could be separated at room temperature into a volatile and a nonvolatile fraction. The volatile fraction consisted of trimethylaluminum $AlMe_3$, hexamethyldisilane $Me_3Si-SiMe_3$, and some octamethyltrisilane $Me_3Si-SiMe_2-SiMe_3$. The nonvolatile fraction, a highly viscous liquid soluble in ether and hexane, contained decamethyltetrasilane $SiMe_3-SiMe_2-SiMe_2-SiMe_3$, in addition to the octamethyltrisilane. The elucidation of the course of the reaction proved to be very tedious and yielded the following information.

At a temperature of 80 °C, the fraction of $Hg(SiMe_3)_2$ which is not decomposed to Hg and $(SiMe_3)_2$ via *(36)* reacts with Al in the expected manner *(35)*, yielding Hg and $Al(SiMe_3)_3$. However, the latter product is unstable under the reaction conditions used and decomposes with liberation of $SiMe_2$ and migration of methyl groups from silicon to aluminum *(37)*, yielding trimethylaluminum $AlMe_3$ and dimethylsilene $SiMe_2$ [13]:

$$Al(SiMe_3)_3 \rightarrow AlMe_3 + 3\ SiMe_2 \qquad (37)$$

The dimethylsilene adds on $SiMe_3$ end groups from $Hg(SiMe_3)_2$, forming higher methylsilanes $SiMe_3-(SiMe_2)_n-SiMe_3$ (where n = 1 or 2). The mechanism is probably similar to that of the Ziegler polymerization of ethylene, the $SiMe_2$ being incorporated into the silylmercury $Me_3Si{\cdot}Hg{\cdot}SiMe_3$ to give the intermediates $Me_3Si{\cdot}Hg{\cdot}Si_2Me_5$ and $Me_5Si_2{\cdot}Hg{\cdot}Si_2Me_5$. These latter then decompose, with expulsion of the Hg atom, producing the observed polysilanes Si_3Me_8 and Si_4Me_{10} [14]. The fact that Si_4Me_{10} is the highest polysilane formed may be explained by the assumption that incorporation of the $SiMe_2$ groups decreases the stability of the mercury silyls to such an extent that they decompose before further groups can be introduced.

2. Reaction of $Hg(SiMe_3)_2$ with $\rangle Al-H$

It has been shown above that the reaction of $Hg(SiMe_3)_2$ with Al according to *(35)* proceeds at a reasonable rate only at 80 °C, a temperature at which the thermal decomposition of $Hg(SiMe_3)_2$ according to *(36)* is already noticeable and at which the $Al(SiMe_3)_3$ desired also decomposes *(37)*. Thus, it became desirable to find an alternative reaction in which the transfer of $SiMe_3$ groups from the $Hg(SiMe_3)_2$ to the aluminum could take place even at room temperature. Reaction according to *(38)*

$$3\ Hg(SiMe_3)_2 + AlH_3 \rightarrow 3\ Hg + Al(SiMe_3)_3 + 3\ SiMe_3H \qquad (38)$$

appeared to offer the possibility of achieving this. To avoid complications due to possible formation of intermediate members of the series such as $AlH_2(SiMe_3)$ and $AlH(SiMe_3)_2$, aluminum hydride as such was not used as the Al–H compound. Instead, its dimethyl derivative Me_2AlH was employed. The latter is easily obtained by methylating AlH_3 (in the form of $LiAlH_4$) with BMe_3 at room temperature.

The reaction at room temperature of $Hg(SiMe_3)_2$ and Me_2AlH (mole ratio 1:1) takes several days. Mercury is liberated and the entire quantity of $Hg(SiMe_3)_2$ is consumed. The overall reaction according to *(39)*

$$Me_2AlH + Me_3Si-Hg-SiMe_3 \rightarrow Hg + Me_2Al(SiMe_3) + Me_3SiH \qquad (39)$$

probably proceeds via an intermediate mercury compound $Me_2Al{\cdot}Hg{\cdot}SiMe_3$. The products are trimethylsilane Me_3SiH (one mole per mole of Me_2AlH), and a dimethylaluminum silyl $Me_2Al(SiMe_3)$ [15]. Like $Al(SiMe_3)_3$ (cf. Section C. I. 1) the aluminum silyl

[12] *O. Stecher*, Ph. D. thesis, Technische Hochschule Karlsruhe, 1939.

[13] A similar decomposition occurs with the corresponding elementally homologous organoaluminum compounds, whereby aluminum trialkyls decompose into trimethylaluminum and an alkene. Thus, upon heating at 200–220 °C in a sealed tube, triisobutylaluminum $Al(C_4H_9)_3$ decomposes to trimethylaluminum (which decomposes further) and propene (which dimerizes and polymerizes):

$$Al(C_4H_9)_3 \rightarrow Al(CH_3)_3 + 3C_3H_6$$

by analogy to *(37)*: *K. Ziegler, K. Nagel*, and *W. Pfohl*, Liebigs Ann. Chem. *629*, 210 (1960).

[14] After the conclusion of this work, the hitherto unknown permethylated polysilanes Si_3Me_8 and Si_4Me_{10} were synthetized at the Munich Institute via a different route: *U. Graf zu Stolberg*, Angew. Chem. *74*, 696 (1962); Angew. Chem. internat. Edit. *1*, 510 (1962).

[15] Some Al_2Me_4 was also formed in a side-reaction as follows

$$Hg(SiMe_3)_2 + 2\ HAlMe_2 \rightarrow Hg(AlMe_2)_2\ (\rightarrow Hg + Al_2Me_4) + 2\ HSiMe_3$$

Like the corresponding tetramethyldiborane B_2Me_4, it disproportionates into trimethylaluminum $AlMe_3$ and elemental aluminum according to the equation

$$3\ Al_2Me_4 \rightarrow 4\ AlMe_3 + 2\ Al.$$

$Me_2Al(SiMe_3)$ proved to be unstable and decomposed *(40)* in a manner analogous to *(37)*

$$AlMe_2(SiMe_3) \rightarrow AlMe_3 + SiMe_2 \qquad (40)$$

yielding trimethylaluminum $AlMe_3$ and dimethylsilene $SiMe_2$. The latter again formed Si_3Me_8 and Si_4Me_{10} by saturation with $SiMe_3$ end groups (cf. Section C.I.1). After removal of the trimethylsilane Me_3SiH formed in reaction *(39)*, the product obtained from the treatment of $Hg(SiMe_3)_2$ with $HAlMe_2$ was a liquid mixture, which was separated further at room temperature into a volatile $AlMe_3$ fraction and a nonvolatile, oily residue consisting of Si_3Me_8 and Si_4Me_{10}. In contrast to the reaction between $Hg(SiMe_3)_2$ and Al at 80 °C, Si_2Me_6 does not occur in the present case, since the decomposition of $Hg(SiMe_3)_2$ shown in *(36)* does not occur at room temperature.

It follows from these studies that the trisilylaluminum compounds $Al(SiR_3)_3$ (where R is an aliphatic substituent), such as $Al(SiMe_3)_3$, are unstable and decompose spontaneously even at room temperature.

$$Al(SiR_3)_3 \rightarrow AlR_3 + SiR_2$$

For the same reason, the existence of even the unsubstituted trisilylaluminum $Al(SiH_3)_3$, corresponding to trimethylaluminum $Al(CH_3)_3$, is at least questionable. The same applies to many other metal silyls of the type $M(SiH_3)_n$ since these, unless they have a saltlike structure, would tend to decompose into silene SiH_2 and the corresponding metal hydrides according to the reaction

$$M(SiH_3)_n \rightarrow MH_n + n\ SiH_2$$

Indeed, the profusion of methyl compounds of the type $M(CH_3)_n$ is certainly not matched by a corresponding abundance of silyl compounds $M(SiH_3)_n$ [16].

II. The Question of the Existence of Tris(triphenylsilyl)aluminum $Al(SiPh_3)_3$ [*]

Metal silyls of the elements of the third group of the periodic table would be expected to be even more prone to ammonolysis by liquid ammonia than those of the first and second groups. This expectation is confirmed by the facts. When aluminum chloride (in the form of $AlCl_3 \cdot NH_3$) is added to a solution of $KSiPh_3$ in liquid ammonia (mole ratio $AlCl_3 : KSiPh_3 = 1:3$), the red-brown solution decolorizes and a white precipitate is formed. The solid obtained on evaporation of the solvent was found to be a mixture of KCl, $SiPh_3H$, $(SiH_3)_2NH$, and Al–N compounds. Thus, it can be concluded that even though the metathesis *(41)*

$$AlCl_3 + 3\ KSiPh_3 \rightarrow Al(SiPh_3)_3 + 3\ KCl \qquad (41)$$

does take place, the desired tris(triphenylsilyl)aluminum $Al(SiPh_3)_3$ is solvolysed *(42)* to triphenylsilane $SiPh_3H$ [17],

$$Al(SiPh_3)_3 + 3\ NH_3 \rightarrow Al(NH_2)_3 + 3\ SiPh_3H \qquad (42)$$

or further *(43)* to hexaphenyldisilazane [18] (cf. Sections A and B).

$$Al(SiPh_3)_3 + 4.5\ NH_3 \rightarrow Al(NH_2)_3 + 1.5\ (SiPh_3)_2NH + 3\ H_2 \qquad (43)$$

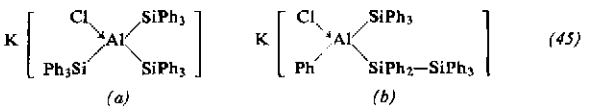
Liquid ammonia is therefore not a suitable medium for the preparation of $Al(SiPh_3)_3$. Nevertheless, this experiment has demonstrated that the $SiPh_3$ groups remain intact in the reaction of $AlCl_3$ with $KSiPh_3$ and that, unlike tris(trimethylsilyl)aluminum $Al(SiMe_3)_3$ (cf. Section C.I), tris(triphenylsilyl)aluminum $Al(SiPh_3)_3$ does not decompose spontaneously into $AlPh_3$ and $SiPh_2$.

Reaction *(41)* was therefore repeated at −20 °C in tetrahydrofuran (THF), which does not cause solvolysis. When a solution of $KSiPh_3$ in THF is added dropwise to a well stirred solution of $AlCl_3$ in THF (mole ratio $AlCl_3 : KSiPh_3 = 1:3$), the dark-brown color of the drops disappears and a white precipitate (KCl) is formed. The amount of KCl is considerably smaller than that expected from *(41)* [19], while the $AlCl_3$ is consumed quantitatively. The missing residue [20] remains "dissolved" in the THF. When the solvent is distilled off, a light-yellow residue is obtained. This is separated with benzene into a colorless, insoluble fraction (A) and a yellowish, soluble fraction (B).

The colorless, benzene-insoluble fraction A is a compound represented by the formula $KCl \cdot Al(SiPh_3)_3$ (yield over 50%). It contains all of the KCl left "dissolved" in the THF and can be redissolved in THF without any residue. It is sparingly soluble in ether, is a reducing agent (reduces $AgNO_3$ to Ag), and evolves hydrogen when treated with ethanolic potassium hydroxide, which reaction indicates the presence of Al–Si bonds. Surprisingly, the amount of hydrogen formed on hydrolysis is only two moles per mole of $KCl \cdot Al(SiPh_3)_3$, whereas three moles of H_2 would be expected from reaction *(44)*.

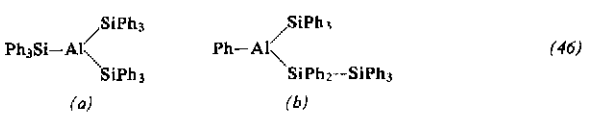
$$KCl \cdot Al(SiPh_3)_3 + 6\ HOH \rightarrow KCl + Al(OH)_3 + 3\ SiPh_3OH + 3\ H_2 \qquad (44)$$

This result can be explained if the compound has structure *(45b)* and not *(45a)*:



(45)

Thus, the tris(triphenylsilyl)aluminum $Al(SiPh_3)_3$ *(46a)* initially formed in reaction *(41)*, is converted into the isomeric form *(46b)* by migration of a phenyl group



(46)

[16] The salt-like compound silylpotassium $K[SiH_3]$ is worth mentioning, since it is one of the few known examples of a well-defined metal silyl of the type $M(SiH_3)_n$ [*M. A. Ring* and *D. M. Ritter*, J. Amer. chem. Soc. *83*, 802 (1961)]. It is electronically isosteric with the equally salt-like and stable compound potassium borohydride $K[BH_4]$.

[*] Experimental work by *H. J. Andrascheck* [1]; Ph = C_6H_5.

[17] Approximately 75% of the $SiPh_3$ groups introduced as $KSiPh_3$ appeared as $SiPh_3H$ under our reaction conditions.

[18] Approximately 25% of the $SiPh_3$ groups introduced as $KSiPh_3$ appeared as $(SiPh_3)_2NH$ under our reaction conditions.

[19] For example, 82% of the theoretical amount of KCl appeared as precipitate.

[20] For example, 18% of the total amount of KCl in "dissolved" form.

from the silicon to the aluminum (cf. the analogous migration of methyl groups in the case of tris(trimethylsilyl)aluminum $Al(SiMe_3)_3$ described in Section C.I). Compound *(46b)* is then complexed by KCl to give compound *(45b)*. Because there are only two Al–Si bonds in the latter, only two moles of H_2 are then evolved on hydrolysis of the compound, since the Si–Si bond is not broken under the mild reaction conditions used.

Interesting results were obtained when *(45b)* was treated with gaseous HCl. One mole of $AlCl_3$ was formed and no H_2 was evolved, while much more HCl [21] was consumed than the three moles expected from formula *(45b)* [cleavage of one Al–C bond and two Al–Si bonds as shown in *(47)*].

$$KCl{\cdot}AlPh(SiPh_3)(Si_2Ph_5) + 3\ HCl \rightarrow KCl + AlCl_3 + HPh + HSiPh_3 + HSi_2Ph_5 \qquad (47)$$

In the experiment, one additional mole of benzene HPh was produced for each mole of HCl above first three [22]. This leads to the conclusion that the HCl is capable of splitting off the phenyl groups bound to silicon, as shown in reaction *(48)*.

$$\rangle Si{-}Ph + HCl \rightarrow \rangle Si{-}Cl + HPh \qquad (48)$$

The reaction is probably catalysed by $AlCl_3$ formed as the by-product. As a result, chlorinated phenylsilanes such as $HSiClPh_2$ and $HSiCl_2Ph$ are formed according to the overall equation *(49)*.

$$KCl{\cdot}AlPh(SiPh_3)(Si_2Ph_5) + (3+n+m)HCl \rightarrow KCl + AlCl_3 + (1+n+m)\,HPh + HSiCl_nPh_{3-n} + HSi_2Cl_mPh_{5-m} \qquad (49)$$

The reaction product resembled silicone grease. The most volatile chlorophenylsilane present was found to be $HSiCl_2Ph$; it was isolated by vacuum distillation of the product at −20 °C and subsequent removal of the accompanying benzene by distillation at −30 °C. The residue of the primary distillation contained the other, less volatile chlorophenylsilanes. When the chlorophenylsilanes obtained in reaction *(49)* were treated with alcoholic KOH, the Si–H bonds were hydrolytically cleaved *(50)* yielding a total of two moles of H_2.

$$2\ \rangle Si{-}H + 2\ HOH \rightarrow 2\ \rangle Si{-}OH + 2\ H_2 \qquad (50)$$

According to the material balance, *the yellowish, benzene-soluble fraction B* from the reaction of $AlCl_3$ with $KSiPh_3$ in THF *(41)* contained $Al(SiPh_3)_3$ free from KCl. Whether the structure *(46a)* or its isomeric formula *(46b)* should be assigned to this aluminum silyl has not yet been determined because the work on this project had to be interrupted for technical reasons. The first alternative *(46a)* is more probable since the structure $Al(SiPh_3)_3$ provides such strong shielding of the Al atom by the three $SiPh_3$ groups that it must remain free of KCl, whereas the isomeric form *(46b)* provides room for complexing with KCl.

[21] For example, 6 moles of HCl were consumed instead of three.

[22] For example, 4 moles of HPh were found instead of 1 mole.

D. Group IV of the Periodic Table

Trimethylsilyltin Compounds R_3Sn-$SiMe_3$ and Related Compounds Containing Sn-Si Bonds [*]

1. Stannylsilanes (Silylstannanes) of the Type $R_3Sn-SiMe_3$

The stannylsilanes (silylstannanes) $R_3Sn-SiMe_3$, which are analogous to ethane, were prepared by treating trimethylchlorosilane $ClSiMe_3$ with tributyltin lithium Bu_3SnLi (or with triphenyltin lithium Ph_3SnLi) in ether at −20 °C. Reaction according to *(51)*

$$R_3SnLi + ClSiMe_3 \rightarrow R_3Sn{-}SiMe_3 + LiCl \qquad (51)$$

produced a precipitate of LiCl and 60–70% yields of $Bu_3Sn-SiMe_3$ (orange-yellow, oily liquid, b.p. 94 °C/1 mm) and $Ph_3Sn-SiMe_3$ (colorless crystals, m.p. 119 °C). When reaction *(51)* took place at +24 °C instead of −20 °C, the yields of stannylsilanes (silylstannanes) $R_3Sn-SiMe_3$ were appreciably reduced and distannanes $R_3Sn-SnR_3$ were formed instead. Thus, reaction between Ph_3SnLi and $ClSiMe_3$ in ether at +24 °C gave only 23% $Ph_3Sn-SiMe_3$. However, the yield of $Ph_3Sn-SnPh_3$ was 54% (both yields are based on Ph_3SnLi). Therefore, the higher temperature favors the competing metal-halogen exchange reaction *(52)* at the expense of the coupling reaction *(51)*,

$$R_3SnLi + ClSiMe_3 \rightleftarrows R_3SnCl + LiSiMe_3 \qquad (52)$$

since the former necessarily precedes the formation of $R_3Sn-SnR_3$ via *(53)*.

$$R_3SnLi + ClSnR_3 \rightarrow R_3Sn{-}SnR_3 + LiCl \qquad (53)$$

2. Bis(stannyl)silanes of the Type $R_3Sn-SiR'_2-SnR_3$

Compounds of the type $R_3Sn-SiR'_2-SnR_3$, which are analogous to propane, were prepared by a coupling reaction similar to *(51)*. The reagents were triorganyltin-lithium compounds R_3SnLi (R = ethyl, butyl, or phenyl) and diorganyldichlorosilanes R'_2SiCl_2 (R′ = methyl or phenyl), and the reaction again took place in ether at −20 °C *(54)*.

$$R_3SnLi + ClSiR'_2Cl + LiSnR_3 \rightarrow R_3Sn{-}SiR'_2{-}SnR_3 + 2\ LiCl \qquad (54)$$

The following compounds were prepared in this manner: $Et_3Sn-SiMe_2-SnEt_3$ (colorless, oily liquid, b.p. 135 °C/1 mm), $Bu_3Sn-SiMe_2-SnBu_3$ (colorless, oily liquid, distills *in vacuo* at 154 °C), $Ph_3Sn-SiMe_2-SnPh_3$ (colorless crystals, m.p. 172 °C), and $Ph_3Sn-SiPh_2-SnPh_3$ (colorless crystals, m.p. 199 °C). The yields were not particularly high (approximately 15% for the two Sn-alkylated compounds and 30–35% for the two Sn-arylated compounds). This fact can be attributed to the existence of a metal-halogen exchange reaction similar to *(52)*,

$$R_3SnLi + ClSiR'_2Cl \rightleftarrows R_3SnCl + LiSiR'_2Cl \qquad (55)$$

which leads to the formation of distannanes $R_3Sn-SnR_3$ (25–30% yield for the first two, 15–20% for the last two bis(stannyl)silanes), as well as higher Sn–Si and

[*] Experimental work by *H. J. Andrascheck* [1]; Me = CH_3, Et = C_2H_5, Bu = $CH_3CH_2CH_2CH_2$, Ph = C_6H_5.

Si–Si chain compounds of decreasing stability. As in the preparation of $R_3Sn–SiMe_3$, the competing formation of $(SnR_3)_2$ compounds becomes dominant at higher temperatures. This was shown by treating Bu_3SnLi with Me_2SiCl_2 and Ph_3SnLi with Ph_2SiCl_2 at room temperature. In each case, only minute quantities of $R_3Sn–SiR'_2–SnR_3$ but large amounts of $R_3Sn–SnR_3$ were obtained [23].

All the $R_3Sn–SiR'_3$ and $R_3Sn–SiR'_2–SnR_3$ stannylsilanes prepared so far dissolve readily as unassociated monomers in nonpolar solvents such as benzene; they are less soluble in ether and are insoluble in ethanol, *i.e.* they possess covalent character. They are all comparatively resistant to atmospheric oxygen, especially the sterically well-shielded phenyl compounds. The liquid members of the series ($Bu_3Sn–SiMe_3$, $Et_3Sn–SiMe_2–SnEt_3$, and $Bu_3Sn–SiMe_2–SnBu_3$) possess an odor typical of many organotin compounds. One of the outstanding properties of the stannylsilanes is their reducing power. This was applied in the preparation of active $TiCl_3$ for Ziegler-type catalysts. For example, a solution of $TiCl_4$ in toluene is added dropwise under a nitrogen blanket to a stirred solution of $Et_3Sn–SiMe_2–SnEt_3$ in toluene (mole ratio silane: $TiCl_4$ = 1:2.5). The reaction is exothermic. The product is a brown precipitate which assumes a brownish-violet color after heating for two hours at 160 °C in a sealed tube (82% yield of $TiCl_3$).

$$(Et_3Sn)_2SiMe_2 + 4\ TiCl_4 \rightarrow 2\ Et_3SnCl\ |\ Cl_2SiMe_2 + 4\ TiCl_3 \qquad (56)$$

The product is thoroughly washed with toluene and petroleum ether. A suspension of the product and Et_2AlCl as co-catalyst in Sinarol® suspension [*] polymerizes ethylene readily [24].

Summarizing, all these initial results obtained with the elements of the first four groups of the periodic system lead to the conclusion that the metal silyls of the type $M(SiR_3)_n$ present no less variety than the corresponding organometallic compounds of the type $M(CR_3)_n$ (where R = hydrogen and/or organic residue). The experimenter may expect an equally large number of compounds and reactions. Further investigations in the field of metal silyls will not only increase our knowledge of valence theory, but may also lead to many practical applications.

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German version: Angew. Chem. 75, 516 (1963)

[23] Thus, 48% $(SnBu_3)_2$ (based on Bu_3SnLi) was formed in the reaction of Bu_3SnLi with Me_2SiCl_2 at room temperature. $SnBu_4$ (21%) was another reaction product; it did not appear at the lower reaction temperature of –20 °C. The reaction of Ph_3SnLi with Ph_2SiCl_2 at room temperature also yielded $SnPh_4$ in addition to $(SnPh_3)_2$.

[*] Sinarol is a mixture of hydrocarbons, b.p. 180–330 °C.

[24] For example, 62 g of polyethylene were obtained using 10 mmoles of $TiCl_3$ catalyst.

Permethylation of Oligomeric and Polymeric Carbohydrates and Quantitative Analysis of the Cleavage Products

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Methylation of mono-, oligo-, and polysaccharides with methyl iodide/barium oxide or dimethyl sulfate/barium hydroxide in dimethyl sulfoxide as solvent rapidly leads to high degrees of methylation. Depending on the structure and solubility of the substrate, permethylation can be achieved either in one operation or by repetition of the same treatment. Procedures for permethylation of various carbohydrates are given. The methyl glycosides obtained on methanolysis can be separated and determined quantitatively by gas chromatography. The preparation of separating columns with minimum retention for this purpose is described. Pullulan was shown to have the structure of a completely linear polymer of maltotriose units connected by α-1→6-linkages. – In addition the gaschromatographic identification of methyl ethers of glucosamine and galactosamine is reported.

Introduction

The structure of a carbohydrate molecule consisting of either a few or of many monosaccharide units depends on the following:

1. The nature of the monomer,
2. the configuration of the glycosidic linkages,
3. the position of the carbon atoms forming the glycosidic linkages,
4. the molecular weight,
5. in the case of macromolecules, the topographic distribution of the different types of bonds.

[*] Communication No. 3 on "Investigations of Pullulan"; Communication No. 2: *H. Bender* and *K. Wallenfels*, Biochem. Z. *234*, 79 (1961).

Even for polysaccharides containing only one type of monomer unit, the elucidation of the distribution of the different bond types in the molecule poses far greater difficulties than the identification of the structure of a protein molecule with 20 or more different constituent amino acids. For this reason it is still not possible to completely define the structure, for example, of the glycogen molecule. The difficulty lies in determining the sequence of the bond types (1 → 4- and 1 → 6-bonds) and the type and number of side chains. The most important method for structural determinations consists of methylating all the hydroxyl groups and then subjecting the polysaccharide to solvolytic cleavage.

A. Methods of Methylation

Mainly *Purdie* and *Irvine* [1] as well as *Haworth* and his co-workers [2] developed methods for permethylating carbohydrates and glycosides that are analogous to the Williamson ether synthesis. These methods mostly employed silver oxide/methyl iodide or dimethyl sulfate/sodium hydroxide, and in special cases also sodium in liquid ammonia/methyl iodide [3]. In general, several concecutive methylations were required to etherify all the hydroxyl groups.

Permethylation of sucrose in one operation was readily achieved with dimethylformamide as solvent [4]. The following methods have proved to be reliable:

I. Methyl iodide with silver oxide a) In dimethylformamide (DMF) [4] (Examples: solanine, tomatine, fructose, lacto-*N*-tetraitol); b) in dimethyl sulfoxide (DMS) [5] (Examples: pullulan [*], starch, dextran).

II. Methyl iodide with barium oxide and/or barium-hydroxide: a) In DMF [7,8] (Examples: *N*-acetyl-lactosaminol, indigo); b) in dimethyl sulfoxide (DMSO) [5]; c) in DMF + DMSO [5].

III. Dimethyl sulfate with barium oxide and/or barium hydroxide. a) In DMF [9]; b) In DMF + DMSO [9] (Examples: inositol, loliin).

Dimethyl sulfate is cheaper and sometimes more effective than methyl iodide. Barium oxide and/or barium hydroxide are generally preferable to silver oxide. Amounts ranging from 50 mg to 20 g of carbohydrates or partially methylated carbohydrates have been treated in the described manner.

Since *meso*-inositol, loliin, soluble starch, pullulan, dextran, and other carbohydrates are practically insoluble in DMF, with these compounds we used method IIb or IIc, with DMSO as solvent, preceded, if nesessary, by preliminary methylation with dimethyl sulfate/NaOH. In numerous cases, we used method IIIb, where the substances are first dissolved in DMSO. However, methylation of large quantities in pure DMSO is not advisable, since the reaction can become too vigorous [10]. In such cases, dilution of the DMSO with DMF (*e.g.* in a 1:1 ratio by volume) is recommendable provided the substrate remains in solution. DMSO melts at 18.7 °C, and, hence, cannot be used undiluted in methylations with dimethyl sulfate (method III), since these reactions are carried out at 0 °C.

Products obtained by known acetylation methods or by acetolysis can be methylated in excellent yields with dimethyl sulfate in the absence of DMSO (method IIIa). (Examples: hexa-*o*-methyl-*meso*-inositol from hexaacetyl-*meso*-inositol; permethylation of pentaacetyl-D-glucosamine to methyl 2-acetamino-2-deoxy-3,4,5-tri-*o*-methyl-β-D-glucopyranoside, yield: 90 %).

Partial Methylation of Pullulan with Dimethyl Sulfate/Sodium Hydroxide

A solution is made of 3 g of pullulan ("residual pullulan") in 30 ml of water, and 100 ml of 38 % sodium hydroxide and 45 ml of dimethyl sulfate are added dropwise at 20 °C with agitation under nitrogen. The dropwise addition is completed in about 6 hours. The mixture is heated at 35–40 °C for further 3 hours, then for 20 min at 100 °C, and finally cooled. The partially methylated polysaccharide floating on the surface of the reaction mixture is recovered by simply picking it off the surface. The liquid is separated from the salts by decantation, diluted to twice its volume with water, and then extracted five times with 200-ml portions of chloroform. The recovered polysaccharide is also dissolved in this chloroform extract. The extract is then thoroughly washed once with water, dried with sodium sulfate, and the chloroform removed by distillation. The residue is dissolved in a very small amount of chloroform, and the resulting solution added dropwise to ice-cold petroleum ether. The partly methylated polysaccharide precipitates as a white, fibrous substance. Yield: 2 g, containing about 32 % OCH_3.

[1] *T. Purdie* and *J. C. Irvine*, J. chem. Soc. (London) *83*, 1012 (1903).

[2] *W. N. Haworth* et al., J. chem. Soc. (London) *1928*, 2681; *W. N. Haworth* and *H. Machemer*, ibid. *1932*, 2270.

[3] *J. E. Muskat*, J. Amer. chem. Soc. *56*, 693, 2449 (1934); *K. Freudenberg* and *H. Boppel*, Ber. dtsch. chem. Ges. *71*, 2435, 2505 (1938).

[4] *R. Kuhn*, *H.Trischmann*, and *I. Löw*, Angew. Chem. *67*, 32 (1955).

[5] *G. Bechtler*, Diploma Thesis, Universität Freiburg, 1960; Ph. D. Thesis, Universität Freiburg, 1962.

[*] Pullulan is a polysaccharide isolated from the slime sheath of *Pullularia pullulans* by filtering the culture medium and precipitating with cold acetone [6]. Dissolution in boiling water and reprecipitation affords a homogeneous polymer ("residual pullulan"), which on enzymatic degradation with pullulanase affords pure maltotriose. Glucose and an oligosaccharide, which together constitute about 8–9% of the pullulan, remain in the supernatant. – Note added in proof: In addition to these minor components, pullulan contains small amounts of amylase (glucamylase type) which causes chromatograms of enzymatic hydrolysates to be misleading (*D. Freudenberger*, Diploma Thesis, Universität Freiburg, 1962). The name pullulane should therefore be applied only to the pure polysaccharide, *i.e.* to "residual pullulan".

[6] *H. Bender*, *J. Lehmann*, and *K. Wallenfels*, Biochim. biophysica Acta *36*, 309 (1959).

[7] *R. Kuhn*, *H. H. Baer*, and *A. Seeliger*, Liebigs Ann. Chem. *611*, 236 (1958).

[8] *R. Kuhn* and *H.Trischmann*, Chem. Ber. *94*, 2258 (1961).

[9] *R. Kuhn* and *H.Trischmann*, Chem. Ber. *96*, 284 (1963).

[10] Dimethyl sulfoxide/methyl iodide gives *inter alia* trimethylsulfoxonium iodide, described by *R. Kuhn* and *H.Trischmann*, Liebigs Ann. Chem. *611*, 117 (1958). The statement above is not valid for partially methylated products.

Remethylation according to Method IIb

A solution of 1 g of this product in 5 ml of DMSO is treated with 10 ml of methyl iodide and 12 g of barium oxide and allowed to stand overnight at 35–40 °C. The treatment with 10 ml of methyl iodide and 12 g barium oxide is repeated, and the mixture again allowed to stand at 35–40 °C for 24 hours. It is then extracted four times with 50-ml portions of chloroform, and the resulting solution worked up as described above.

The light-yellowish residue is dissolved in a very small amount of chloroform. The resulting viscous syrup is then diluted with benzene to a very fluid solution. On running this solution into ice-cold petroleum ether, the permethylated polysaccharide is obtained as a white powder containing 45.6 % OCH_3. Yield: 800 mg. Its infrared spectrum shows no hydroxyl band (see Fig. 9d).

Dextran (Knoll 100) [*] and starch (Amylum solubile, Merck) were methylated in the same manner with equally good results. Yield of permethylated product: 650 mg from 1 g of starch, and 700 mg from 1 g of dextran.

The above methods are limited on the one hand by the solubilities in DMSO and DMSO/DMF mixtures of the compounds to be methylated (untreated cellulose, untreated starch, pullulan, and indanthrene cannot be permethylated by method III), and on the other by the sensitivity to alkali of the glycosidic linkages, amide groups, *etc.* (1 → 3-linked disaccharides consisting of two hexose units would undergo hydrolysis; glycolipids give small amounts of fatty acid methyl ester; sialic acid residues undergo partial cleavage).

With some substrates, *e.g.* soluble starch, method III yields products having a low sulfur content (about 1 %), presumably carbohydrate methyl sulfates. In these cases, methods IIb or IIc are preferred. Finally, hydrogen bonds can markedly complicate methylation, at least the one-step permethylation (by method III, alizarin yields mainly the 2-methyl ether and only a small amount of the 1,2-dimethyl derivative, whereas method IIa affords the latter compound in about 15 % yield).

Further peculiarities are encountered with reducing sugars. With glucose, lactose, and other oligosaccharides containing glucose residues as the reducing group, so far only the permethylated pyranose derivatives have been isolated. However, methylation of fructose by method I, gave 50–60 % penta-*o*-methyl-D-fructofuranose [11]. Reducing galactose residues in the furanose form also undergo permethylation [12]. Figures 1 and 2, and Figures 3 and 4 show the proportions in which α- and β-penta-*o*-methylglucose and α- and β-octa-*o*-methyllactose are formed from glucose and lactose, respectively.

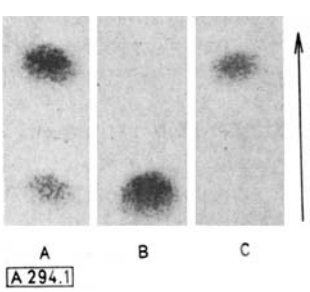

Fig. 1. Thin-layer chromatograms of (A) methylated glucose, (B) methylated methyl α-glucoside, and (C) methylated methyl β-glucoside. The direction of migration is indicated by the arrow. Methylation was carried with $(CH_3)_2SO_4$, according to method IIIa.

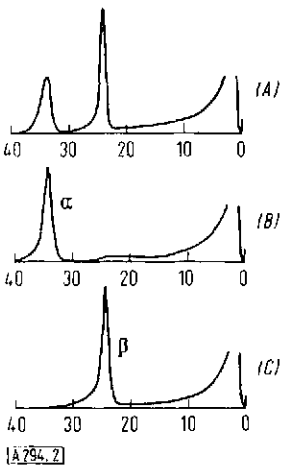

Fig. 2. Gas chromatograms of (A) methylated glucose, (B) methylated methyl α-glucoside, and (C) methylated methyl β-glucoside (according to experiments by *H. Egge*). Chromatography was carried out at 200 °C on a Celite-packed column containing 20 % poly(butane-1,4-diol succinate). (Column length: 2 m; diameter: 4.6 mm) Carrier gas: Helium Gas flow rate: 100 standard ml/min. Pressure: 2 atm.

Abscissa: Time [min].

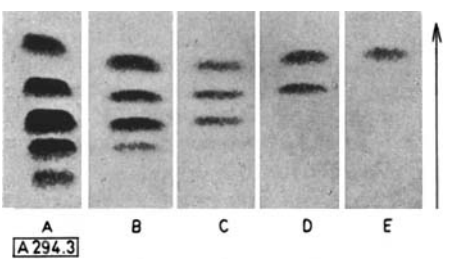

Fig. 3. Thin-layer chromatograms of methylated lactose (the arrow indicates the direction of migration).

A = Following one methylation according to *Haworth* [12a] (46.2 % by weight methoxyl)

B = After two methylations according to *Haworth* [12a] (50.3 % by weight methoxyl)

C = After three methylations according to *Haworth* [12a] (52.8 % by weight methoxyl)

D = After one methylation with $(CH_3)_2SO_4/Ba(OH)_2$ in DMF method IIIa) (54.3 % by weight methoxyl)

E = Crystalline β-octamethyllactose (54.5 % by weight methoxyl; calcd.: 54.6 %)

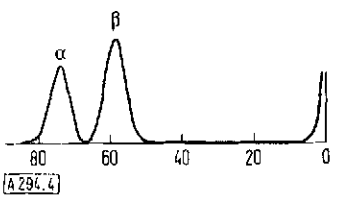

Fig. 4. Gas chromatogram of sample D in Figure 3 (lactose permethylated by method IIIa; α- and β-octamethyllactone). For operating conditions see legend under Fig. 2.

Abscissa: Time [min].

meso-Inositol yields four products on single methylation with $(CH_3)_2SO_4/NaOH$ but can be permethylated in one operation with $(CH_3)_2SO_4/BaO/Ba(OH)_2$ in DMF/

[*] We wish to thank the Knoll AG., Ludwigshafen (Germany), for providing us with a sample of this material.

[11] *R. Kuhn* and *H. Grassner*, Liebigs Ann. Chem. *610*, 122 (1957).

[12] *W.T. J. Morgan*, personal communication.

[12a] Methylation procedure: *W. N. Haworth* and *G. C. Leitch*, J. chem. Soc. (London) *113*, 188 (1918).

DMSO (1:1) at 0–20 °C (Fig. 5). In the latter case, the hexamethyl ether of *meso*-inositol (m.p. 18 °C) is obtained in 85 % yield.

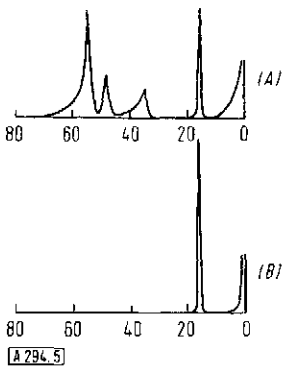

Fig. 5. Gas chromatogram of methylated inositol (according to experiments by *H. Egge*).
A = Inositol, methylated once with $(CH_3)_2SO_4$/sodium hydroxide
B = Inositol, methylated once with $(CH_3)_2SO_4$/BaO/$Ba(OH)_2$ in DMF:DMSO (1:1) at 0–20 °C.
For operating conditions see legend under Fig. 2.
Abscissa: Time [min].

The methylation products were studied by thin-layer chromatography as follows. A slurry of 30 g of Silica Gel G (Merck) in 60 ml of water was applied to five 20×20 cm^2 glass plates. The plates were dried for 5 hours at 130 °C. Six to eight spots were then applied at 2-cm intervals at a distance of 3–4 cm from the edge by means of drawn out melting point capillaries. Ascending chromatography, with a mixture of 200 ml of benzene and 40 ml of absolute ethanol as eluant, was used. Time: 1–1.5 hours. The plates were dried and sprayed with 50 % sulfuric acid and then heated for about 20 min at 130 °C.

B. Determination of the Methoxyl Content of Methylated Polysaccharides

Any polysaccharide consisting of only hexose units has the general formula $H-(C_6H_{10}O_5)_n-OH$; hence, the corresponding permethylated polysaccharide has the formula $CH_3-(C_9H_{16}O_5)_n-OCH_3$. It follows that, for high molecular weights ($n > 300$), the calculated, theoretical methoxyl value is 45.6 % by weight. At lower molecular weights, the influence of the two CH_3O groups at the reducing and non-reducing end of the molecule gradually becomes more pronounced (Fig. 6).

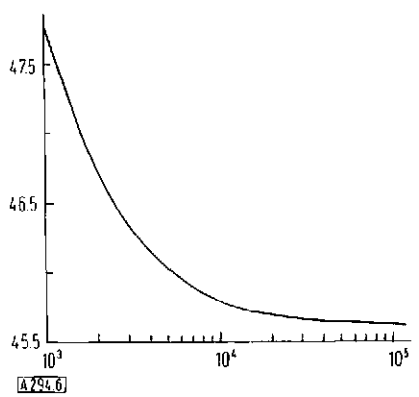

Fig. 6. Correlation between molecular weight and methoxyl content for methylated polyhexoses.
Ordinate: Methoxyl content of permethylated polysaccharide [% by wt.]
Abscissa: Molecular weight of the permethylated polysaccharide.

The accuracy of the methoxyl determinations on about 20 mg of substance can be improved to ± 0.1–0.2 % by standardization of the working procedure [*]. Using the apparatus of *Vieböck* and *Schwappach* [13] and iodometric titration [14], we found a CH_3O content of 45.5 ± 0.1 % for permethylated pullulan.

Hydrolysis of the permethylated polyhexose yields 1 mole of dimethylated and 1 mole of tetramethylated hexose (from the non-reducing end of the side chain) for each branching point. The correlation between the per cent of dimethylated hexose and the degree of branching is depicted in Figure 7.

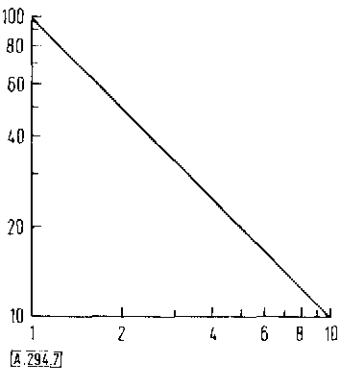

Fig. 7. Correlation between the number of points of branching in a polyhexose and the proportion of dimethylated hexose in the hydrolysate from the permethylated polysaccharide.
Ordinate: Glucose residues per branching point.
Abscissa: Dimethylglucose [% by wt.].

Figure 8 shows the variation of the methoxyl content on incomplete, random methylation of a polyhexose with an assumed molecular weight of 100000. An actual methoxyl content of, for example, 0.5 % less than the theoretical value of 45.6 % indicates that, on the average, one hydroxyl group per 26 hexose units remained unmethylated; this corresponds to a content of 3.9 % dimethylated hexose in the hydrolysate. Thus, a degree of branching similar to that found for amylopectin would be simulated. This emphasizes the importance of complete methylation and the need for an accurate analytical methoxyl determination.

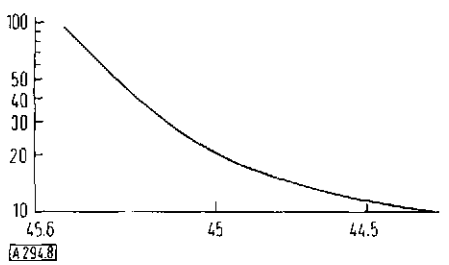

Fig. 8. Branching simulated by incomplete methylation.
Ordinate: Glucose residues per apparent branching point.
Abscissa: Methoxyl content of the methylated polysaccharide [% by wt.]

[*] Analytical result of the Freiburg group.

[13] *F. Vieböck* and *A. Schwappach*, Ber. dtsch. chem. Ges. *63*, 2818 (1930).
[14] *F. Vieböck* and *C. Brecher*, Ber. dtsch. chem. Ges. *63*, 3207 (1930).

Free hydroxyl groups can be estimated by infrared spectroscopy. This method enables one to check the completeness of methylation (Fig. 9). Solid methylation products are dissolved in absolutely dry carbon tetrachloride; the spectra of syrupy materials can be obtained without the use of a solvent. Glassy solids can be

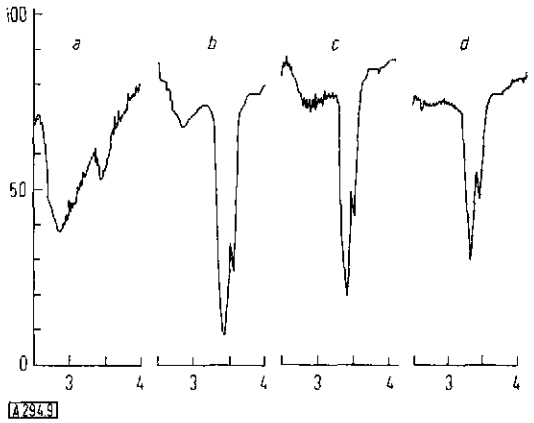

Fig. 9. Parts of infrared spectra of methylated and nonmethylated "residual pullulans".
(a) "Residual pullulan"
(b) "Residual pullulan", partly methylated (32 % OCH_3)
(c) Sample b, remethylated (45 % OCH_3; 1 % hexose dimethyl ether in hydrolysate)
(d) Sample c, remethylated (45.6 % OCH_3; 0.1–0.2 % hexose dimethyl ether in hydrolysate).
Ordinate: Transmission [%]
Abscissa: Wavelength [μ].

fused and a thin layer applied to a sodium chloride plate. In the absence of moisture, fully methylated compounds no longer show absorption bands in the 2.8 to 2.9 μ region (Fig. 9d). The infrared spectrum of an incompletely methylated polysaccharide, on the other hand, exhibits a definite OH band even if the hydrolysate of this linear polysaccharide contains only 1 % hexose dimethyl ether (Fig. 9c).

If some of the hydroxyl groups are esterified with methylsulfuric acid, no OH bands are found despite considerable undermethylation (established by methoxyl determination). In these cases a sulfur determination will suffice for a correct interpretation of the results.

C. Cleavage and Quantitative Determination of the Methylated Monomers

The reducing sugars formed on hydrolysis of methylated oligo- and polysaccharides can be determined by paper chromatography. The methyl glycosides, obtained by heating the free sugars with 2 % methanolic hydrochloric acid at 80–85 °C for 24–90 hours, lend themselves to gas-chromatographic determination.

1. Determination of Methylated Monomers by Paper Chromatography

Reversed-phase chromatography [15] effects complete separation, for example, of 2,3,4- and 2,3,6-tri-*o*-methylglucose, as well as separation of each of the two monosaccharides into the α- and β-form (Fig. 10). No other chromatographic method described so far has this separating capacity.

Fig. 10. Paper-chromatographic separation of 2,3,4- and 2,3,6-tri-*o*-methylglucose (the arrow indicates the direction of migration).
I: 2,3,4-tri-*o*-methylglucose
II: 2,3,4- and 2,3,6-tri-*o*-methylglucose (hydrolysate from permethylated pullulan).
III: 2,3,6-tri-*o*-methylglucose.

Practical Procedure

Sheets of Whatman No. 1 paper are dipped into a mixture of toluene and dimethyl sulfoxide (5:1), quickly pressed between sheets of filter paper, and then allowed to hang for 1 min in a drying cabinet at 60 °C. This impregnation is repeated, and the paper is then stored between two glass plates. To apply the sugar samples, the paper sheet is pulled out from between the plates a little beyond the starting line. Solutions of the samples in chloroform are then applied at spots 40 mm apart. Diisopropyl ether saturated with dimethyl sulfoxide at the temperature of the chromatography tank is employed as eluent and lower phase. Ascending chromatography in a jar with a ground-glass cover is used. To test for tetra-*o*-methylglucose, the run must be interrupted after 6 hours. To separate the tri-*o*-methylglucoses from each other and from di-*o*-methylglucose, the run is extended to 40–48 hours. The chromatogram is dried in a stream of air at 100 °C and then sprayed uniformly on both sides with a 2.5 % solution of aniline phosphate (a 1:1 molar mixture of freshly distilled aniline and crystalline phosphoric acid) in glacial acetic acid [16]. The sheets are allowed to hang for 2 minutes to ensure uniform distribution of the reagent and are then kept at 100 °C for 3 minutes. The sugars appear as brown or red-brown spots. Quantitative determination is achieved by excising the spots, eluting each with 5 ml of a freshly prepared mixture of n-butanol and conc. hydrochloric acid (5:2), clarifying the extracts by filtration and, after 3 hours, examining them colorimetrically at 405 mμ. The reference cell contains a similarly prepared extract of blank paper. Results are reproducible to within ± 5 %.

2. Gas-Chromatographic Determination of Methylated Monomers

The most suitable stationary phase material [17–20] is partly methylated hydroxyethylcellulose [19]. Chromosorb W was used most frequently as support. Even under optimum conditions, hydroxyethylcellulose of varying degrees of methylation still showed strong retention which became increasingly evident when the degree of

[15] *B. Wickberg*, Acta chem. scand. *12*, 615 (1958).

[16] *L. Hough, J. K. N. Jones*, and *W. H. Wadman*, J. chem. Soc. (London) *1950*, 1702.

[17] *C. D. Chang* and *H. B. Hass*, J. org. Chemistry *23*, 773 (1958).

[18] *S. W. Gunner, J. K. N. Jones*, and *M. B. Perry*, Chem. and Ind. (London) *1961*, 255.

[19] *H. W. Kircher*, Analytic. Chem. *32*, 1103 (1960).

[20] *M. Gee* and *H. G. Walker jr.*, Analytic. Chem. *34*, 650 (1962).

loading was reduced (to increase the number of theoretical plates). This lead to broad, often unsymmetrical bands, which did not lend themselves to quantitative evaluation even if satisfactory separation was achieved. *Gee* and *Walker* [20] encountered the same difficulty and, therefore, gave up their attempts at quantitative evaluation. The strong retention of hydroxylated compounds, when Chormosorb is used, is presumably due to its great internal surface area.

Retention disappeared nearly completely when we used glass beads as support. By varying the loading and the column length, we obtained columns which, with a programmed temperature rise from 140 to 155 °C, made it possible to separate the methyl tri-*o*-methyl-glucosides (without the disturbing band broadening or shifting of the base line). The separation efficiency decreases, *i. e.* the number of theoretical plates per unit length of the column, rapidly increases with increasing column length [*].

To detect traces of tetramethylated and dimethylated methyl glucosides, we used a 1.20 m coiled column; a 3 m long column of the same type was used for trimethylated methyl glucosides. The chromatograms were quantitatively evaluated according to the triangle method [21]; the percent composition was determined by the internal standard method. Results for the main bands were reproducible to within ± 1–2 %.

Practical Procedures

Preparation of Partly Methylated Hydroxyethylcellulose

A highly viscous solution of 10 g of hydroxyethylcellulose [**] in 150 ml of water was methylated with 150 ml of dimethyl sulfate and 425 ml of 37 % sodium hydroxide. The reaction mixture was extracted three times with 300 ml of chloroform, washed twice with water, and evaporated to dryness. The residue was dissolved in benzene/chloroform and precipitated with petroleum ether. The substance (about 9 g) was dissolved in 75 ml of dry dimethylformamide and heated with 2 g of anhydrous calcium sulfate, 50 ml of methyl iodide, and 35 g of silver oxide. After the exothermic reaction had subsided, the mixture was heated at 40 °C. After 24 hours, it was extracted with 500 ml of chloroform and the extract filtered, washed once with $NaHSO_3$ solution and then twice with water. After evaporating the chloroform, the residue was dissolved in benzene and reprecipitated with petroleum ether. In this manner, 4.5 g of white, partly methylated hydroxyethylcellulose with a methoxyl content of about 30 % were obtained.

Preparation of the Column Packing

The methylated hydroxyethylcellulose was dissolved in benzene, dry, degreased glass beads were added, and the mixture was concentrated to a paste in a rotary evaporator. The benzene was then distilled off *in vacuo*, with frequent shaking, until the mass started to stick together. The material was then spread out in Petri dishes and crushed with a spatula until the beads no longer adhered to each other. Proper operation yields a dry, non-smeary product. The beads prepared in this manner were heated for 24 hours at 100 °C, with occasional turning, then washed with petroleum ether, filtered, and again kept at 140 °C for 6 hours.

Packing of the Columns

Steel columns, equipped with Swagelock fittings, are easy to pack. Water aspirator vacuum was applied to one end of the column through tubing, connected to it by means of a brass adaptor containing a fine-mesh screen on the inside. The column was then packed from the other end by means of a small funnel. Glass wool was then introduced at both ends. The packing uniformity is reproducible even for 3-meter columns.

Gas-Chromatographic Separation

Support: Glass beads, 0.3 mm ⌀ [*]. Active phase: partially methylated hydroxyethylcellulose. Coverage: 4 mg/g, 135 mg per meter of column. Length of coiled columns: 0.6, 1.2, and 3 m. Column temperature: 140–155 °C. Temperature programming: 1.6 °C increase per minute. Injection port temperature: 270 °C. Detector temperature: 280 °C. Helium flow rate: 21–22 standard ml per minute. Detector sensitivity: 1.

D. Application to Special Structural Problems

1. Examination of Monosaccharide Mixtures

The method for separating anomeric methyl glucosides permits direct determination of the composition of equilibrium mixtures; this could previously be calculated only from rotational measurements. Furanosides and anhydro sugars present in such mixtures can also be determined. After treatment for 40 hours with 2 % methanolic HCl at 85 °C, the following compounds were detected:

In the methyl 2,3,4-tri-*o*-methylglucoside mixture: 74 % α-methyl pyranoside, 25.6 % methyl β-pyranoside, and 0.4 % 2,3,4-tri-*o*-methylglucosan;

In the methyl 2,3,6-tri-*o*-methylglucoside mixture: 61.9 % methyl α-pyranoside, 34.7 % methyl β-pyranoside, and 3,4 % methyl furanoside.

2. Proof for the Structure of 2,3,6-Tri-o-methyl-1,4-anhydroglucose

This new substance [22] and its known isomer, 2,3,4-tri-*o*-methyl-1,6-anhydroglucose, give coinciding chromatograms, both containing only a single band. After methanolysis, both chromatograms exhibited two new bands. For the unknown product, these bands corresponded to those of methyl 2,3,6-tri-*o*-methyl-α- and -β-glucosides. This proves that the new substance is 2,3,6-tri-*o*-methyl-1,4-anhydroglucose.

[*] The theoretical plate height, determined with methyl 2,3,4-tri-*O*-methyl-β-glucoside for 0.6, 1.2, and 3 m columns, was found to be 0.35, 0.60, and 1.38 mm, respectively.

[21] *A.T. James*, Methods biochem. Analysis *8*, 1 (1960).

[**] Hydroxyethylcellulose with a degree of substitution of about 1.34 was kindly furnished by Dipl.-Chem. *E. Siefert* of the Institut für Makromolekulare Chemie der Universität Freiburg/Brsg. (Germany).

[*] From Glaswerke Wertheim (Germany).

[22] *E. Husemann* and *J. Klar*, Makromolekulare Chem. *53*, 223 (1962).

3. Structure of Maltotriose

Enzymatic hydrolysis of "residual pullulan" [23] with pullulanase from *Aerobacter aerogenes* affords a quantitative yield of maltotriose as the only oligosaccharide. Unequivocal proof of this structure, was, however, lacking. The permethylated product obtained by method IIb, was subjected to methanolysis and the resulting product chromatographed on a 1.2 m column as described in section C (see Fig. 11). Quantitative

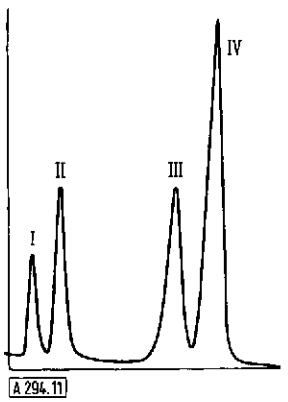

Fig. 11. Gas chromatogram of the product of methanolysis of methylated maltotriose. Operating conditions (see section C 2):
140—150 °C; Δt = 1.6 °C/min; column: 1.2 m long
I: Methyl 2,3,4,6-tetra-*o*-methyl-β-D-glucoside
II: Methyl 2,3,4,6-tetra-*o*-methyl-α-D-glucoside
III: Methyl 2,3,6-tri-*o*-methyl-β-D-glucoside
IV: Methyl 2,3,6-tri-*o*-methyl-α-D-glucoside

evaluation (33.5 % methyl 2,3,4,6-tetra-*o*-methylglucoside and 66.5 % methyl 2,3,6-tri-*o*-methylglucoside) proved that two 1 → 4 linkages are present in the maltotriose.

4. Structural Investigations of Polysaccharides

a) "Residual Pullulan"

The type of bonds joining the trisaccharide units in pullulan were established only after quantitative analysis of the product of methanolysis from permethylated "residual pullulan" (Fig. 12), which indicated 0.6 % methyl 2,3,4,6-tetra-*o*-methylglucoside, 31.9 % methyl 2,3,4-tri-*o*-methylglucoside, 67.3 % methyl 2,3,6-tri-*o*-methylglucoside, and 0.2 % methyl di-*o*-methylglucoside (determined from a second gas chromatogram with increased injection dosis).

The amount of methyl tetra-*o*-methylglucoside found shows that slight degradation to a molecular weight of 50000 takes place on methylation. Similar degradation was also observed when residual pullulan was heated with very dilute acid [24]. The presence of only 0.2 % methyl dimethylglucoside indicates the complete linearity of residual pullulan. Hence, the latter consists of glucose chains with regular alternation of two α-1 → 4 and one α-1 → 6 linkage.

[23] *H. Bender* and *K. Wallenfels*, Biochem. Z. *334*, 79 (1961).
[24] *K. Wallenfels* and *G. Keilich*, unpublished data.

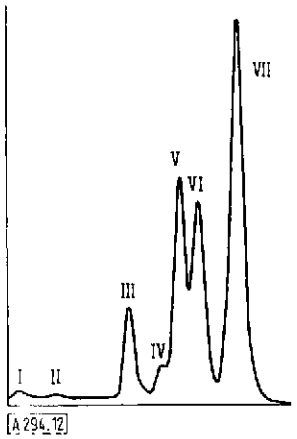

Fig. 12. Gas chromatogram of the product of methanolysis of permethylated pullulan. Operating conditions (see section C 2):
140—155 °C; Δt = 1.6 °C/min; column: 3 m long.
I: Methyl 2,3,4,6-tetra-*o*-methyl-α-D-glucopyranoside
II: 2,3,4-tri-*o*-methyllevoglucosan
III: Methyl 2,3,4-tri-*o*-methyl-β-D-glucopyranoside
IV: Methyl 2,3,6-tri-*o*-methylglucofuranoside
V: Methyl 2,3,6-tri-*o*-methyl-β-D-glucopyranoside
VI: Methyl 2,3,4-tri-*o*-methyl-α-D-glucopyranoside
VII: Methyl 2,3,6-tri-*o*-methyl-α-D-glucopyranoside

b) Soluble Starch

Permethylated soluble starch was subjected to methanolysis for 24 hours. Gas chromatography then showed 5.2 % methyl 2,3,4,6-tetra-*o*-methylglucoside, 89.9 % methyl 2,3,6-tri-*o*-methylglucoside, and 4.9 % methyl 2,3-di-*o*-methylglucoside.

c) Dextran

The composition of the product of methanolysis of permethylated dextran showed no further changes after 90 hours of methanolysis. The proportions of tetra-, tri-, and dimethylated methylglucosides were determined on a 1.20 m column (Fig. 13). The methyl tri-*o*-methylglucoside fraction was separated into its components on a 3 m column (Fig. 14).

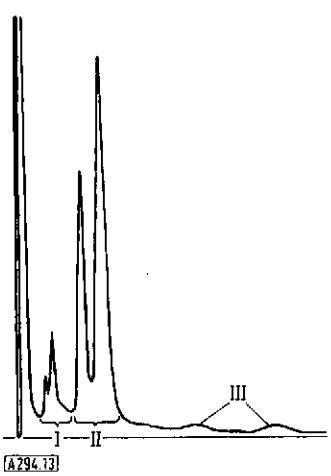

Fig. 13. Gas chromatogram of the product of methanolysis of permethylated dextran. Operating conditions (see section C 2):
isothermal run at 180 °C; column: 1.2 m long.
I: Methyl 2,3,4,6-tetra-*o*-methyl-D-glucoside (7.1 %).
II: Methyl tri-*o*-methyl-D-glucoside (81.8 % methyl 2,3,4-tri-*o*-methylglucoside and 4.4 % methyl 2,3,6-tri-*o*-methylglucoside).
III: Methyl di-*o*-methylglucoside (6.7 %).

The methyl di-*o*-methylglucoside fraction (III in Fig. 13) is not identical with methyl 2,3-di-*o*-methylglucoside. According to *Whelan* [25], dextran contains considerable amounts of 1 → 3 linkages. Therefore, we suspect that

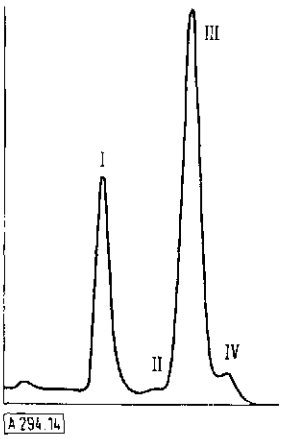

Fig. 14. Gas chromatogram of methyl tri-*o*-methylglucosides from permethylated dextran (fraction II of chromatogram shown in Fig. 13). Operating conditions (see section C 2): 140—150 °C; Δt = 1.6 °C/min; column: 3 m long.
I: Methyl 2,3,4-tri-*o*-methyl-β-D-glucoside
II: Methyl 2,3,6-tri-*o*-methyl-β-D-glucoside
III: Methyl 2,3,4-tri-*o*-methyl-α-D-glucoside
IV: Methyl 2,3,6-tri-*o*-methyl-α-D-glucoside

this fraction is methyl 2,4-di-*o*-methylglucoside and originates from the glucose residues involved in branching. The presence of methyl 2,3,6-tri-*o*-methylglucoside and the absence of the 2,3-dimethyl ether show that the 1 → 4 linkages are present in the main chain and not in the side chains.

E. Addendum

Identification of Methyl Ethers of Glucosamine and Galactosamine by Gas Chromatography [*]

Methods are known for separating volatile derivatives of hexoses (methyl ethers [26—31], peracetylated compounds [32], trimethylsilyl ethers [33], and others [34]).

We attempted to apply these methods to derivatives of amino sugars. Methyl *N*-acetylhexosamides proved to be suitable for this purpose; any free hydroxyl groups were acetylated. These compounds volatilize at 120 to

Table 1. Retention times [a] relative to methyl *N*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucosaminide = 1.0 on a 1 m column filled with 10 % polyester on silicic acid at 228 °C and 210 ml of He per min.

Substance	Retention index[35]	Relative retention time	M. p. [°C]	Ref.
Methyl *N*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucosaminide	3015	1.00 [b]	153—154	[36]
Methyl *N*-acetyl-3,4,6-tri-*O*-methyl-β-D-glucosaminide	3110	1.37 [b]	199	[37] [c]
Methyl *N*-acetyl-4,6-di-*O*-methyl-3-*O*-acetyl-α-D-glucosaminide	3050	1.13	109—110	[d]
Methyl *N*-acetyl-3,6-di-*O*-methyl-4-*O*-acetyl-α-D-glucosaminide	3285	2.53	163	[e]
Methyl *N*-acetyl-3,4-di-*O*-methyl-6-*O*-acetyl-α-D-glucosaminide	3335	3.00	171	[36]
Methyl *N*-acetyl-3-*O*-methyl-4,6-di-*O*-acetyl-α-D-glucosaminide	3555	6.27	167—168	[38]
Methyl *N*-acetyl-3,4,6-tri-*O*-methyl-α-D-galactosaminide	3095	1.31 [b]	185—186	[39]
Methyl *N*-acetyl-3,4,6-tri-*O*-methyl-β-D-galactosaminide	3195	1.82 [b]	232	[39] [f]
Methyl *N*-acetyl-4,6-di-*O*-methyl-3-*O*-acetyl-α-D-galactosaminide	3145	1.56	111—112	[40]
Methyl *N*-acetyl-3,4-di-*O*-methyl-6-*O*-acetyl-α-D-galactosaminide	3420	3.95	202—203	[40]
1,6-Anhydro-*N*-acetyl-3,4-di-*O*-methyl-β-D-galactosamine	3050	1.12	108—110	[40]

[a] The values given are the mean values from at least 3 chromatograms. The maximum deviation was ± 2 %.

[b] In contrast to the methyl glycosides of methylated glucoses and galactoses, here the methyl α-glycosides run faster than the corresponding β-anomers.

[c] This compound is also obtained by direct methylation of *N*-acetylglucosamine according to *R. Kuhn, H. Trischmann,* and *I. Löw* [41].

[d] This compound was obtained by preparative-scale gas chromatography from permethylated *lacto-N*-tetraose [42].

[e] This compound was obtained by preparative gas chromatography from permethylated *N*-acetyllactosamine [43] after methanolysis and reacetylation.

[f] Methyl *N*-acetyl-3,4,6-tri-*O*-methyl-β-D-galactosaminide is also formed in 10 % yield by direct methylation of *N*-acetylgalactosamine in dimethylformamide with $BaO/Ba(OH)_2$ and dimethyl sulfate.

[25] *W. J. Whelan*, Bull. Soc. Chim. biol. *42*, 1570 (1960).

[*] By *R. Kuhn* and *H. Egge* and *W. Lochinger*. Reported in part by *R. Kuhn* at the 4th International Congress on Gas Chromatography in Hamburg (Germany) on June 13th, 1962, and by *H. Egge* at the Colloquium on Gas Chromatography in Karlsruhe (Germany) on Sept. 6th, 1961.

[26] *A. G. McInnes, D. H. Ball, F. P. Cooper*, and *C.T. Bishop*, J. Chromatogr. *1*, 556 (1958).

[27] *H.W. Kircher*, Analytic. Chem. *32*, 1103 (1960).

[28] *C.T. Bishop* and *F. P. Cooper*, Canad. J. Chem. *38*, 388 (1960).

[29] *C.T. Bishop* and *F. P. Cooper*, Canad. J. Chem. *38*, 793 (1960).

[30] *G. A. Adams* and *C.T. Bishop*, Canad. J. Chem. *38*, 2380 (1960).

[31] *E. Bayer:* Gas-Chromatographie. Springer, Heidelberg 1962, p. 133.

[32] *J. K. N. Jones* and *S.W. Cramer*, Chemistry and Industry *1961*, 255.

[33] *R. Kaiser:* Chromatographie in der Gasphase. Bibliographisches Institut, Mannheim (Germany) 1962, Vol. III, p. 29.

[34] *C.T. Bishop* in *D. Glick:* Methods of Biochemical Analysis. Interscience, New York 1962, Vol. X, p. 1.

[35] *A. Wehrli* and *E. Kovats*, Helv. chim. Acta *24*, 2709 (1959).

[36] *R.W. Jeanloz*, J. Amer. chem. Soc. *74*, 4597 (1952).

[37] *W. O. Cutler, W. N. Haworth*, and *S. Peat*, J. chem. Soc. (London) *1937*, 1979.

[38] *R. Kuhn, H. H. Baer*, and *A. Seeliger*, Liebigs Ann. Chem. *611*, 236 (1957).

[39] *M. Stacey*, J. chem. Soc. (London) *1944*, 272.

[40] *R.W. Jeanloz, D. M. Schmidt*, and *P. J. Stoffyn*, J. Amer. chem. Soc. *79*, 2586 (1957).

[41] *R. Kuhn, H. Trischmann*, and *I. Löw*, Angew. Chem. *67*, 32 (1955).

[42] *R. Kuhn* and *H. H. Baer*, Chem. Ber. *89*, 504 (1956).

[43] *R. Kuhn* and *W. Kirschenlohr*, Chem. Ber. *87*, 560 (1954).

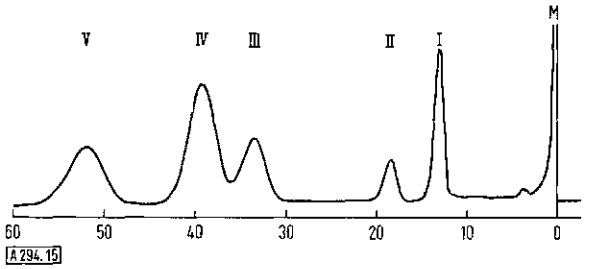

Fig. 15. Quantitative analysis of a synthetic mixture of substances I–V in 93 mm³ of methanol; 3 mm³ of solution injected into a 1 m column of 10 % polyester on kieselghur at 226 °C; 212 ml of He per min.
M = methanol
Abscissa: time [min]

		Weight inserted G_S [mg]	Area under peak (estimated by weighing G_P [mg]	G_P/G_S
I	Methyl *N*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucosaminide	5.45	15.3	2.81
II	Methyl *N*-acetyl-3,4,6-tri-*O*-methyl-β-D-glucosaminide	2.12	6.1	2.88
III	Methyl *N*-acetyl-3,6-di-*O*-methyl-4-*O*-acetyl-α-D-glucosaminide	5.43	15.2	2.80
IV	Methyl *N*-acetyl-3,4-di-*O*-methyl-6-*O*-acetyl-α-D-glucosaminide	10.71	30.0	2.80
V	Methyl *N*-acetyl-3,4-di-*O*-methyl-6-*O*-acetyl-α-D-galactosaminide	7.70	20.5	2.67

150 °C/1×10⁻³ mm and are readily obtainable in about 80% yield from permethylated oligo- or polysaccharides by methanolysis and subsequent reacetylation (during the methanolysis some of the *N*-acetyl groups are split off). The derivatives of glucosamine and galactosamine examined had been characterized by melting points, analyses, and comparison of their infrared spectra with those of authentic samples.

The columns used for the gas chromatography were 1 m long and were filled with 8–10 % of a butanediol/succinatepolyester [28] distributed on kieselghur in conjunction with a Perkin-Elmer 116 E instrument. Before impregnation with the liquid phase, the kieselghur (E. Merck – for gas chromatography) was stirred for 3 hours at 80 °C with 2N NaOH, washed with distilled water until neutral, then stirred with conc. HCl for 3 hours at 80 °C and rewashed until the eluate was free from chloride ions. The kieselghur was then dried at 160 °C and the fraction with grain diameters of 0.125 to 0.175 sieved off for use.

Temperatures of 200–250 °C and flow speeds of 70–202 ml of He per min were used. The retention times lay between 15 and 120 min. Our results are summarized in Table 1; Figure 15 illustrates a typical separation.

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Further Contributions to the Knowledge of Semimetals

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Dedicated to Dr. W. Foerst on the occasion of his 65th birthday

Measurements on semimetals have been continued. Studies of the dependence on temperature of various properties have provided details regarding the transition from the nonmetallic to the more metallic structure. A second-order transition has been found for tin at 170 °C, in which the c-axis remains unchanged, while the a-axis undergoes a small, discontinuous elongation.

As *Klemm* and *Kubaschewski* [1a] have shown, there is a definite boundary between metals with high and semimetals with low lattice coordination numbers, as seen in Figure 1.

However, this applies only to the solid state. At the melting point, transitions to more closely packed forms occur in the borderline elements Si, Ga, Ge, Sb, and Bi. In tin, this transition is already found in the solid state as the transformation from the gray (β) to the white (α) form. In As and Te, the situation is more complicated, while phosphorus on melting forms a melt consisting

Mg	Al	Si	P	S
Zn	Ga	Ge	As	Se
Cd	In	Sn_{gray} / Sn_{white}	Sb	Te
Hg	Tl	Pb	Bi	Po

A 299.1

Fig. 1. Borderline between metallic and nonmetallic structures in the periodic system (after [1a]).

[1a] *W. Klemm*, Angew. Chem. *62*, 133 (1950); *O. Kubaschewski*, Trans. Faraday Soc. *45*, 931 (1949).

of P_4 molecules. To characterize these transitions we carried out the measurements reported previously [1b]. We are now able to report additional results that provide a clearer picture of the phenomena.

1. Elements of Group IV of the Periodic Table

One important question concerns the principles governing the transition from the nonmetallic to the more metallic form in this group. The clearest illustration is tin. Here statements can be made with exceptional confidence, since the two forms of tin occur in the solid state, and the structure of a crystal can be established with much greater accuracy than the structure of a melt. Gray tin crystallizes in the diamond structure. The lattice structure of white tin is unusual and cannot be considered to be a purely metallic structure with any degree of certainty. It can be derived formally from the diamond structure.

To do this, the diamond lattice must be compressed in the direction of one of its axes. This compression is severe: the c/a ratio in a section of the diamond structure corresponding to the tin lattice is 1.41; the ratio for white tin is only 0.54. It is characteristic of the diamond structure that each atom is tetrahedrally surrounded by four others; the distance to more distant neighbors is very much greater. On compression of the diamond structure to that of white tin, the tetrahedral linkage involving sp^3 bonding is approximately preserved, but the tetrahedron is compressed in the direction of a square. Thus, two atoms that were originally remote approach almost to the same interatomic distance as that of the four nearest neighbors. For a c/a axial ratio of 0.52, all six neighbors are equidistant from the central atom. In white tin, which has a c/a ratio of 0.54, four neighbors are found at distances of 3.02 Å and two others at distances of 3.18 Å. The coordination polyhedron is, however, still considerably far from being a regular octahedron.

There is also a change in the interatomic distances during the transformation from gray to white tin; this corresponds to the general experience that interatomic distances are functions of the coordination number. For a transition from a coordination number of 4 to a coordination number of 6, the distances should change by 6–7 % according to *Goldschmidt*. Actually, the change in distance of the four nearest neighbors amounts to 8 %, while the distance of the two other atoms changes by 13 %.

Thus, we can discern two principles that give rise to the white tin lattice:

1. the sp^3 bonds of gray tin are strongly distorted;

2. this distortion is necessary that the number of nearest neighbors can increase (from 4 to 6).

In the white tin lattice, therefore, two trends coexist: a tendency to form directed interatomic bonds is maintained – a typical characteristic of nonmetals – and a tendency to attain the maximum possible coordination number in order to approximate a metal is also in operation.

Alternatively one can, as, for example, *Krebs* has done, derive the lattice structure of white tin from the simple cubic packing, however, necessarily with strong distortion towards the diamond lattice, so that the 6 "nearest" neighbors are disposed as 4 + 2. Even more in keeping with a simple cubic packing are the lattices of bismuth and tellurium. Here the different degree of distortion corresponds to the different number of coordination bonds involved, whereby the 6 "nearest" neighbors may be partitioned as 3 + 3 or 2 + 4. It is only through these bonding effects that it is possible for a structure of such low packing density as the simple cubic lattice to be even approximately attained.

Molten tin probably has essentially the same structure as white tin. *H. Krebs* [1c] presently investigates this, but the evaluation of his results is not yet complete.

We assume that on melting germanium [2] and silicon similar changes occur as on the transition of gray tin into white. From the measurements of atomic distances in molten germanium performed by *Krebs* [1c] and from our own previous density measurements, we conclude that the structure of a germanium melt is closer to the diamond structure than that of tin and that directly above the melting point, the arrangement of the 4 + 2 neighbors, as far as the angles and distances are concerned, correspond to a structure of the same kind as that of white tin, although the axial ratio c/a = 0.63. The compression for silicon is probably even smaller. That the angles of molten Ge and Si do not deviate as far from the tetrahedral angle as those of white tin would be in good agreement with the fact that the temperatures of transition from the diamond structure to structures similar to that of white tin lie substantially higher than the temperature for tin (Ge 950 °C, Si 1410 °C).

Second-Order Transition of Tin

The first-order transition from gray to white tin is followed at higher temperatures (between 150 and 200 °C) in the solid state by a second-order transition that is clearly manifest in the change in mechanical properties. It was assumed earlier that a transition to a rhombic form was involved [3]. Although this assumption has long been discarded, strangely enough it still finds its way into many text books. *Bartenev* [4] found an anomaly in the temperature dependence of the specific heat at about 165 °C; however, little note has been taken of this observation.

We first determined the change in the lattice constants with temperature and found (Fig. 2) that from room temperature up to the neighborhood of the melting point the c-axis of the tetragonal lattice increases in length quite smoothly, while, in contrast, the length of the a-axis is suddenly, albeit only slightly, changed at about 170 °C. The tetragonal lattice is thus retained,

[1b] *W. Klemm, H. Spitzer,* and *H. Niermann,* Angew. Chem. *72,* 985 (1960).

[1c] *H. Krebs,* personal communication.

[2] To supplement the data on the properties of liquid germanium [1b], it seems appropriate to append a fact or two concerning its magnetic behavior. In melts, this element departs from the diamagnetism characteristic of nonmetals and assumes a paramagnetic condition. The χ_{atom} value of $+ 4\times10^{-6}$ to $+ 5\times10^{-6}$ for molten germanium is virtually the same as that of white tin ($\chi_{atom} = + 3\times10^{-6}$). Note added in proof: More accurate values for the magnetic susceptibility of Germanium in the solid and liquid state have been published by *G. Busch* and *S. Yuan,* Phys. kondes. Materie *1,* 37 (1963).

[3] *C. O.Trechmann,* Mineralog. Mag. J. mineralog. Soc. *3,* 186 (1860); *H.v. Foullon,* Jahrb. k. k. Reichsanst. *1884,* 367.

[4] *G. M. Bartenev,* Zh. tekh. Fiz. *17,* 1321 (1947).

but the c/a ratio decreases somewhat. This second order transition is strongly reminiscent of the relationships found for arsenic above 200 °C. Thus, just as for As, we also studied the temperature dependence of certain other properties of Sn. In the enthalpy curve, we observed a slight, abrupt rise at about 175 °C, followed

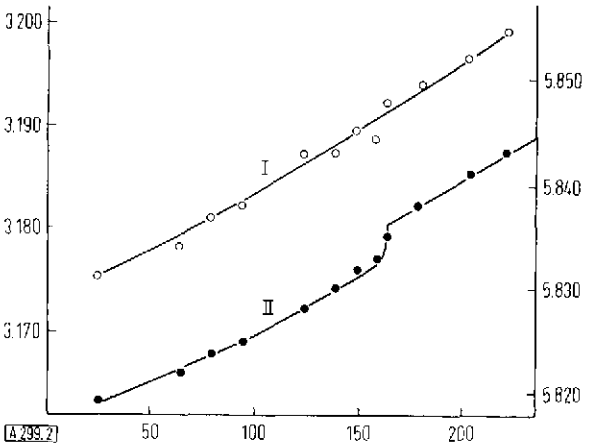

Fig. 2. Dependence on temperature of the lattice constants of white tin.
Curve I: c-axis
Curve II: a-axis
Ordinate: left: length of the c-axis [kX] [*]
right: length of the a-axis [kX] [*]
Abscissa: Temperature [°C]

by a flatter stretch (Fig. 3), so that at higher temperatures the results practically fit a linear extrapolation of the data between 100 and 170 °C. Thus, our results can be reconciled with those, for example, of *Schübel* [5] and *Spring* [6], who in making measurements over wider temperature intervals, were not aware of this

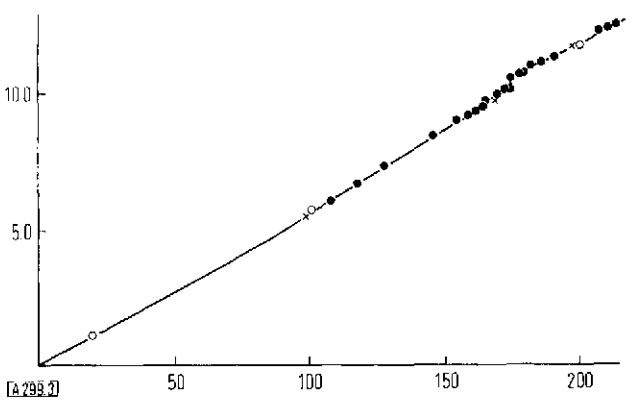

Fig. 3. Temperature dependence of the enthalpy of white tin.
o = *Schübel*'s values [5].
× = *Spring*'s values [6]
• = our values.
Ordinate: Enthalpy [cal/g]
Abscissa: Temperature [°C].

effect (cf. Fig. 3). On the other hand, apart from a small temperature difference, our findings agree with those of *Bartenev* [4].

B. Predel [6a] studied the tin/lead system between 170 and 180 °C at the Institut für Metallkunde of the University of Münster using differential thermal analysis, and found a similar weak thermal effect, which was surprisingly only slightly detectable in pure tin. Thus, the thought arose that perhaps these effects might be caused by a slight contamination of the tin by lead. However, our investigations using ultrapure tin and tin lightly alloyed with lead have convinced us that the lead content has no effect on measurements of the lattice constants and the conductivity (see below).

Subsequently we put a great deal of effort into determining the dependence on temperature of the electrical conductivity of tin [6b]. In most cases we found that the conductivity showed a small, abrupt decrease at the transition temperature. However, there were a few examples where small increases were observed at this temperature. Figure 4 shows a selection of our experimental results.

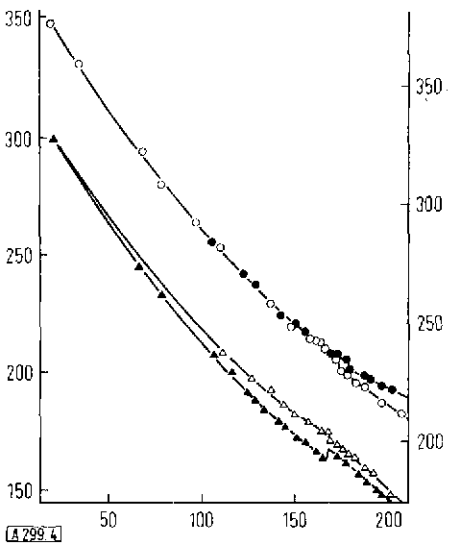

Fig. 4. Dependence on temperature of the electrical conductivity of white tin.
First series of measurements: o = falling temperature
• = rising temperature; left ordinate
Second series of measurements: Δ = falling temperature
▲ = rising temperature; right ordinate
Ordinate: Scale divisions [arbitrary units]
Abscissa: Temperature [°C]

It was difficult to reproduce the measurements; in many cases, nearly identical values were obtained on increasing and decreasing the temperature, but occasionally the conductivity curves were quite different in the two directions. We had previously experienced this phenomenon with arsenic. It might be concluded from this that, in Sn and As, the relatively small changes in the lattice constants and enthalpy may be involved with changes in bond relationships that exhibit hysteresis effects. Special experiments would be required to establish whether tempering for longer periods of time might give more reproducible results. Obviously for accurate measurements of the electrical conductivity of even the purest tin, the pretreatment of the sample must be carefully taken into account.

The behavior of the magnetic properties with temperature is peculiar. The weak paramagnetism of white tin increases a little as the temperature rises up to about 150 °C. It then remains constant or even decreases a little (Fig. 5). These differences, however, lie just

[*] 1 kX-unit = 1.00202 Å.

[5] *P. Schübel*, Z. anorg. allg. Chem. *87*, 82 (1944).

[6] *W. Spring*, Bull. Acad. Belgique (3) *11*, 355 (1886).

[6a] We wish to remark with gratitude at this point, that Dr. *B. Predel* also investigated arsenic by the method of differential thermal analysis and observed an effect at 200–220 °C. In our earlier communication, we neglected to mention this.

[6b] For the method of measurement see [1b].

outside the limits of the accuracy of measurement. We were unable to observe an inflection in the curve near 170 °C.

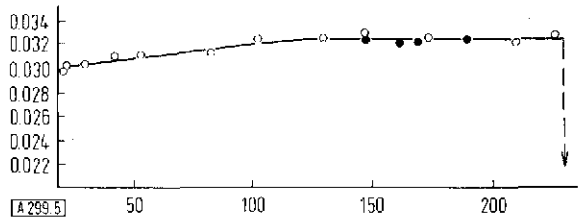

Fig. 5. Dependence on temperature of the magnetism of white tin.
o = rising temperature
• = falling temperature
Ordinate: Specific susceptibility $\chi_g \times 10^6$ [cm³/g]
Abscissa: Temperature [°C]

In summary, we can say that the long-known change in the properties of white tin at high temperature is related to a second-order transition at 170 °C. At this temperature, the a-axis of the lattice is altered, there is a sudden increase in the enthalpy (by about 50 cal/g-atom), and the conductivity shows a small change; the magnetic properties are only slightly affected. Although these effects are comparatively small, the change in the mechanical properties indicates that the alterations of electronic structure must be rather profound.

2. Elements of Group V of the Periodic Table

Phosphorus

Among the elements phosphorus, arsenic, antimony, and bismuth, the first-named occupies a unique position, since red phosphorus, on heating, passes over into a melt which is composed of P_4 molecules and which is in every way identical with the melt obtained from white phosphorus. This phenomenon has been discussed thoroughly in the previous communication [1b].

For completeness, we have studied the magnetic properties of the modifications of phosphorus over a wide range of temperature (Fig. 6). Solid red phosphorus shows diamagnetism that is virtually independent of temperature. It is slightly smaller than that of white phosphorus which possesses the same χ_{atom} value in

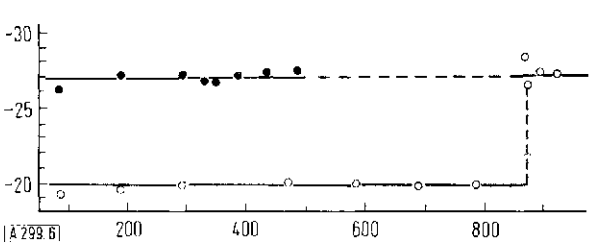

Fig. 6. Dependence on temperature of the magnetism of white and red phosphorus.
o = white phosphorus
• = red phosphorus
Ordinate: Specific atomic susceptibility $\chi_{atom} \times 10^6$ [cm³/g]
Abscissa: Temperature [°K]

both the liquid and solid states. The diamagnetism of the melt obtained from red phosphorus is exactly the same as the diamagnetism of white phosphorus at low temperatures.

In addition, we have determined the enthalpies of red and white phosphorus as well as the heat of fusion of red phosphorus. The results are shown in Fig. 7. The

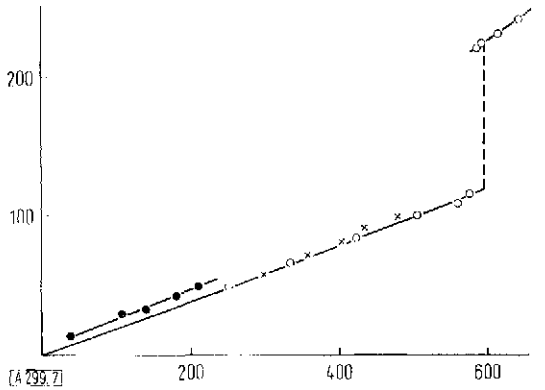

Fig. 7. Dependence on temperature of the enthalpy of phosphorus.
× = *Kubaschewski* and *Schrag*'s values [7]
o = our values for red phosphorus
• = our values for molten white phosphorus
Ordinate: Enthalpy [cal/g]
Abscissa: Temperature [°C]

atomic heat capacity of red phosphorus rises somewhat with temperature; the average atomic heats amount to 6.11 (0–200 °C), 6.21 (0–400 °C), and 6.39 (0–500 °C) cal/deg/g-atom. The heat of fusion is $3.1_9 \pm 0.1$ kcal/g-atom, and the entropy of fusion is 3.6_6 e.u./g-atom.

Correction to room temperature gives 3.8_5 kcal/g-atom for the heat of fusion. If the heat of fusion of white phosphorus (0.16 kcal/g-atom) is subtracted from this value, we obtain 3.7 ± 0.1 kcal/g-atom as the heat of transition of white phosphorus into red, which is in satisfactory agreement with the value of 4.2 ± 0.2 kcal/g-atom calculated by *Rodewald* [8] from vapor pressure curves.

Arsenic, Antimony, and Bismuth

The processes taking place in solid arsenic (second-order transition), the heat of fusion, and the specific heat and electrical conductivity of the molten material have already been reported [1b]. With regard to the electrical conductivity of the melt, it might be added that we were able to follow its behavior with temperature up to 1050 °C. The specific resistance drops from *ca.* 390×10^{-6} ohm·cm at the melting point to 280×10^{-6} ohm·cm at 1050 °C, and appears to pass through a minimum at that temperature; measurements at higher temperatures were not possible, because the walls of the vessel could not withstand the increased pressure. The volume change on melting has also been reported in the previous communication [1b].

As further characteristic data, we determined the density of the melt over a wide temperature range and measured the magnetic behavior on the same sample.

[7] *O. Kubaschewski* and *G. Schrag*, Z. Elektrochem. angew. physik. Chem. *46*, 675 (1940).

[8] *H. J. Rodewald*, Helv. chim. Acta *43*, 878 (1960).

We measured the density by observing the change in the meniscus in the small tube used for the magnetic measurements. This is certainly not very accurate, but suffices for characterization. Thus, at 820 °C, a density of 5.05 g/cm³ was found; *Spitzer* [1b] previously obtained 5.08 ± 0.05 g/cm³ [*]. Since arsenic is easily supercooled, we were able to make measurements down to 50 °C below its melting point. Figure 8 shows the

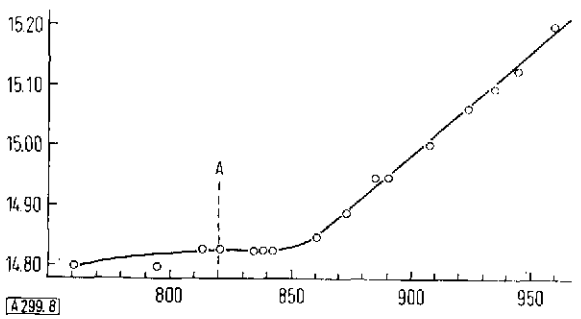

Fig. 8. Dependence on temperature of the atomic volume of molten arsenic.

A = melting point
Ordinate: Atomic volume [cm³]
Abscissa: Temperature [°C]

atomic volume curve. It is seen that from 760 to 850 °C there is practically no change, and then the volume begins to increase linearly. If this linear portion of the curve is extrapolated to room temperature, an atomic volume of about 12.2 cm³ is obtained, *i.e.* a value even smaller than that of α-arsenic (13.1 cm³).

The magnetic behavior is reproduced in Figure 9. The diamagnetism of solid arsenic increases with increasing temperature and then falls off abruptly at the melting point. In the melt, the diamagnetism decreases further and gradually passes over into weak paramagnetism.

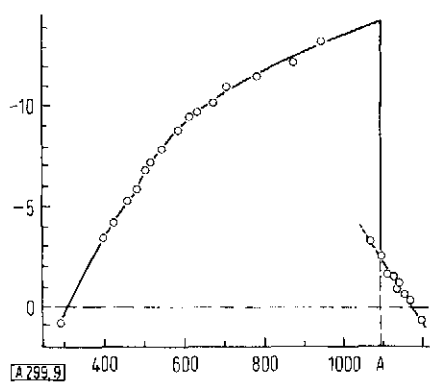

Fig. 9. Dependence on temperature of the magnetism of solid and molten arsenic.

A = Melting point
Ordinate: $\chi_{atom} \times 10^6$ [cm³/g]
Abscissa: Temperature [°K]

In continuation of our studies on antimony, we have also measured the enthalpy of a supercooled antimony melt. It is seen from Figure 10 that the enthalpy curve of the melt is deflected downward at lower temperatures as it supercools; *i.e.* on cooling a melt below the melting point, exothermic processes occur.

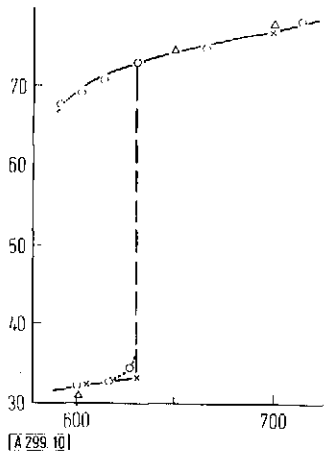

Fig. 10. Dependence on temperature of the enthalpy of solid and liquid antimony and of the supercooled melt.

o = our values; Δ and × = values from the literature [8a].

Ordinate: Enthalpy [cal/g]
Abscissa: Temperature [°C]

The Behavior of Arsenic, Antimony, and Bismuth on Melting

For all three elements, a change of structure is involved in the melting process, just as with Ga, Ge, and Si: the layer lattice is transformed into a more closely packed arrangement of atoms with a structure more similar to those of metals [8b]. The fact that a structure change is involved is shown, for example, by the large values of the entropy of fusion. These amount to 4.7 e.u./g-atom for arsenic according to our measurements [8c], 5.3 e.u./g-atom for antimony, and, from the literature, 5.1 e.u./g-atom for bismuth [8d]. Many authors have already emphasized that such high entropies of melting are characteristic of semimetals. Likewise, the ratios of the coefficients of expansion in the solid and molten state are characteristic of semimetals. According to *Schneider* and *Heymer* [9], these ratios lie between 0.20 and 0.40, while for pure metals and meta-metals, values between 0.73 and 1.04 are found. These values are already established for antimony and bismuth (for both, about 0.30); we obtained a value of 0.23 for arsenic, using the high-temperature values for the melt. Individually, however, the transition to the melt is different for the three elements (cf. Table 1). If the transition in As at 200 to 250 °C is disregarded, there

[*] Note added in proof: Recently *P. I. McGonigal* and *A.v. Grosse*, J. physic. Chem. *67*, 924 (1963), have published density measurements of liquid arsenic. Their values are by about 4% higher than the values published here.

[8a] Cf. *S. Umino*, Sci. Rep. Tōhoku Imp. Univ. *15*, 604 (1904); *F. Wüst*, *A. Meuthen*, and *R. Durrer*, Forschungsarb. Gebiete Ingenieurwes. *204*, 40 (1918).

[8b] A model for the formation of the "metallic" structure – as for tin in Group IV – is unfortunately unavailable in Group V. Atomic distribution functions for Bi and Sn have been measured by *H. K. F. Müller* and *H. Hendus*, Z. Naturforsch. *12a*, 102 (1957), and by *H. Krebs* [1b].

[8c] In this case, no allowance has been made for thermal effects just above the melting point. If they are taken into account, a value of 5.1 e.u./g-atom is obtained for the entropy of fusion.

[8d] *W. Oelsen*, *O. Oelsen*, and *D.Thiel*, Z. Metallkunde *46*, 555 (1955).

[9] *A. Schneider* and *G. Heymer*, Naturwissenschaften *46*, 167 (1959).

is no hint in the solid state of the structural changes encountered on melting. The volume change on melting is positive and at 10 % is quite large.

From this it must be concluded that, on melting, the double-layered structure of solid arsenic is partially preserved, but that the layers lose their mutual ordering and drift apart; *i.e.* effects are encountered similar to those reported by *Krebs* [10], who made X-ray studies of the transition $\alpha \rightarrow \beta \rightarrow \gamma$-arsenic. It is easily seen that this assumption is not in itself sufficient, but that further processes must occur: the transition from α- to β- and to γ-arsenic is related to a substantially greater volume change (15–20 %) than is observed in the melt. Moreover, the assumption of layer displacement alone cannot properly explain the large entropy of fusion. Again, the diamagnetism should increase on melting, since β-arsenic is more strongly diamagnetic than α-arsenic [11]. Another consequence would be that the melt would then display poor conductivity, since according to *Klemm* and *von Falkowski* [12], the conductivity of β-arsenic is at least ten orders of magnitude lower than that of α-arsenic. Now, it is true that molten arsenic conducts more poorly than solid arsenic at the melting point; however, the resistivity is only doubled. Thus, an additional process must occur on melting. Apparently, the layers are partially broken up, and, in the melt even at the melting point, portions assume a somewhat more metallic structure. This fraction with "metallic" structure, which corresponds to a closer packing, rapidly increases as the temperature rises above the melting point. This phenomenon manifests itself in that, at first, no thermal expansion takes place, the resistivity decreases, and the diamagnetism is also reduced and passes over into weak paramagnetism such as is characteristic of metals. Especially characteristic is the variation with temperature of the specific heat, which has a maximum just above the melting point.

The greatest part of the processes involved in the transition take place between the melting point (818 °C) and 850 °C. However, the transition processes are certainly still not complete at that upper limit (cf. magnetism and conductivity). It must be assumed that transition into the more metallic form is still not completely attained even at 1000 °C.

Table 1. Behavior of some semimetals in the vicinity of the melting point.

	Volume change	Caloric behavior		Resistivity [10^{-6} ohm · cm]		Magnetism Specific atomic susceptibility, [$\chi_{atomic} \times 10^6$]	
		atomic enthalpy of fusion [kcal/g-atom]	atomic entropy of fusion [e.u./g-atom]	solid	liquid	solid [cm³/g]	liquid [cm³/g]
Arsenic m.p. 818 °C	$\Delta V = +10$ % Volume of the melt first constant, then increasing	5.1	4.7	205	390	Decreases from +1 at room temperature to −14 at m.p.	−3 With increasing temperature changes to weak paramagnetism
		Maximum of the specific heat of the melt above the freezing point		In the melt resistivity decreasing to 280 (minimum ?)			
Antimony m.p. 630 °C	$\Delta V = +1$ %	4.8	5.3	158	109	−45	−2
		In the solid state, immediately below the freezing point, increase of specific heat. In the supercooled melt, maximum in the specific heat below the freezing point		In the solid state, increase of resistivity with temperature just below the m.p. In the melt, only a small increase with temperature		Anomalous diamagnetism in the solid state [*]	
Bismuth m.p. 271 °C	$\Delta V = -3$ %	2.7	5.1	290	127	−200	−8
						Strong anomalous diamagnetism in the solid state [*]	
Tellurium m.p. 450 °C	$\Delta V = +5$ % Minimum in the melt near the m.p.	4.1	5.7	8000	550	−36	−3
		In the supercooled melt, below the m.p., maximum in the specific heat		In the melt, resistivity first falls sharply, minimum at 900 °C, then weak increase			

[*] The diamagnetism decreases strongly, even before the melting point is reached. The figures given are valid for the beginning of this decrease.

The situation is different with antimony. Here the transition to the more metallic form obviously occurs much more easily than with arsenic, since the melting point, at which the transition takes place, is lower. The change in structure is already foreshadowed in the solid state, since there is an inflection in the resistivity curve even well below the melting point. The enthalpy also increases immediately before the true melting point; the entropy of fusion is somewhat larger than the value for arsenic. The volume change on melting is positive, but only slightly so. It must be concluded from this data that a large part of the transition already occurs during the process of melting. Obviously, even here the change in structure is not yet complete at melting [12a];

[10] *H. Krebs* and *F. Schultze-Gebhardt*, Z. anorg. allg. Chem. *283*, 263 (1956).

[11] *H. Stöhr*, Z. anorg. allg. Chem. *242*, 138 (1939).

[12] *W. Klemm* and *I.V. Falkowski*, Z. anorg. allg. Chem. *256*, 343 (1948).

[12a] Note added in proof: *B. Predel*, Z. Metallkunde *54*, 206 (1963), recently found "after-melting effects" for Sb and other semimetals, *i.e.* exothermic changes occurring in the melt after the actual liquefaction is complete.This again shows that melting of such materials is a complicated process which involves intermediate steps. It is not yet clear whether the effects observed by *Predel* are related to the attainment of equilibrium; possibly they are irreversible changes which can be evaluated only dynamically. On cooling no similar alterations occur previous to solidification.

if it were, the volume change on melting would have to be negative. The electrical conductivity increases somewhat on melting; the temperature coefficient of resistivity in the melt is small. This suggests that the conditions at the melting point of antimony correspond roughly to those of arsenic at about 200 °C above its melting point. The behavior of supercooled antimony is also characteristic: the enthalpy curve is strongly depressed; *i.e.* exothermic processes occur on cooling. With regard to its specific heat, supercooled liquid antimony thus resembles molten arsenic just above the melting point.

Finally, for bismuth fusion, *i.e.* the transition to a more metallic state, occurs at relatively low temperature. So far, no anomalous behavior below the melting point has been noted, except that the anomalous diamagnetism starts to decrease before the melting point is reached. The melt conducts electrical current considerably better than the solid material at the melting point. The scanty results available on the resistivity of the melt also show a very slight dependence on temperature. This indicates that here, too, the transition is not yet complete on melting. Our own studies have not encompassed bismuth.

3. Tellurium

Measurements on tellurium have already been discussed in the previous communication [1b]. For the sake of completeness, we have reproduced its enthalpy *vs.* temperature curve in Figure 11. The values for the solid

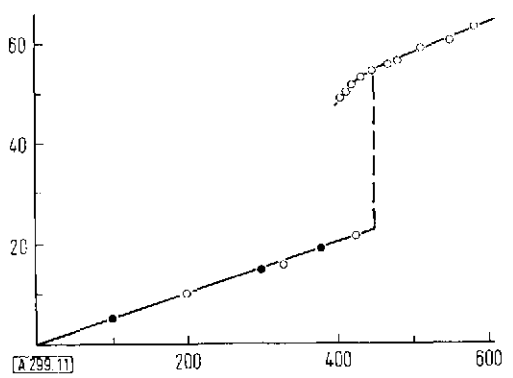

Fig. 11. Dependence on temperature of the enthalpy of solid and molten tellurium and of the supercooled melt.
• = *Tilden*'s values [13]
o = our values
Ordinate: Enthalpy [cal/g]
Abscissa: Temperature [°C]

state are in good agreement with those of *Tilden* [13]. For the heat of fusion, we found $4.1_8 \pm 0.15$ kcal/g-atom, whereas *Kubaschewski* and *Wittig* [14] reported 4.05 ± 0.15 kcal/g-atom. The entropy of fusion is 5.7 e.u./g-atom. Above the melting point, there is nothing striking in the enthalpy behavior of the melt; below the melting point the picture is similar to that for antimony. In addition we have studied the electrical conductivity of molten tellurium over a wide range of temperatures (see Figure 12), using the same basic absolute value as used by *Kraus* and *Johnson* [15], who studied the conductivity of the melt up to 500 °C. Our values are in

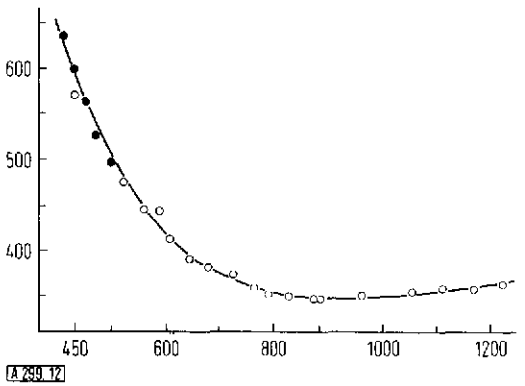

Fig. 12. Dependence on temperature of the resistivity of molten tellurium.
• = values of *Kraus* and *Johnson* [15]
o = our values
Ordinate: Resistivity [10^6 ohm·cm]
Abscissa: Temperature [°C]

agreement with those of the American authors. *Epstein* and co-workers [16] found a minimum in the resistance between 630 and 650 °C but did not make measurements at higher temperatures. Our measurements were extended to 1220 °C. Between 800 and 900 °C, the resistivity passes through a minimum and then slowly rises again.

The behavior of tellurium is thus intermediate between that of arsenic and that of antimony. As with these elements, on supercooling, the melt shows a transition below the melting point from the "chain" structure to the "metallic" form. In the same region, the melt shows a negative coefficient of expansion and the entropy *vs.* temperature curve is strongly inflected. These processes continue in the melt, as the conductivity curve shows; this behavior is very similar to that of arsenic, but here it can be followed over a wider region. In Te above 900 °C, an increase in the resistivity with temperature, such as is characteristic of metallic melts, is observed; we believe this occurs also in As at temperatures above those we measured. It is of interest that Russian investigators have found [17] that below the melting point, the resistivity of solid tellurium decreases (as is also observed in antimony), thus portending the melting process to a certain degree.

4. Concluding Remarks

Upon reviewing the phenomena that take place in semimetals on varying the temperature, we arrive at the following conclusions (see Table 1):

[13] *W. A. Tilden*, Philos. Trans. Roy. Soc. London, Ser. A, *203*, 141 (1904).

[14] *O. Kubaschewski* and *F. E. Wittig*, Z. Elektrochem. angew. physik. Chem. *47*, 433 (1941).

[15] *C. A. Kraus* and *E.W. Johnson*, J. physic. Chem. *32*, 1289 (1928).

[16] *A. S. Epstein, H. Fritsche*, and *K. Lark-Horowitz*, Physic. Rev. (2) *107*, 412 (1957).

[17] *A. I. Blum, N. P. Mokrovski*, and *A. R. Regel*, Izvest. Akad. Nauk SSSR, Ser. Fiz. *16*, 139 (1952).

1. With increasing temperature, transitions occur from a nonmetallic structure of low coordination number to a more metallic structure of higher coordination [18].

2. Only in tin does this transition already take place in the solid state; in the other cases, the melting point coincides with the transition point. The entropy of fusion is always large; the volume change on melting is generally negative (Ga, Si, Ge, Bi) or very slightly positive (Sb); the rather large expansion of As and the normal value for Te are exceptional and depend on the fact that the structural transformations occurring there on melting are incomplete.

3. The structural changes can be initiated (As) or completed (Sn) by second-order transitions in the solid state.

4. The transitions are not complete on melting; they often continue to a greater or less degree above the melting point (especially for As, but also for Te, and possibly for Sb and Bi) [19].

5. The transition to a more metallic form may already be anticipated in the solid state below the melting point (Sb), or evidence for the pertinent structural changes may be found in the supercooled melt (Sb, Te).

6. The fact that semimetal melts can frequently be supercooled with particular case, may be due to the structural changes occurring on melting and solidifying.

Finally, Figure 13 summarizes the electrical conductivity of Si, Ge, As, Bi, and Te. Melts of these elements do not differ significantly in conductivity. The differences do not even amount to a factor of ten. This demonstrates the great similarities among these melts with regard to electrical behavior. Matters are different in the solid state. Si, Ge, and Te are typical semiconductors, whereas As, Sb, and Bi have metallic conduction. Correspondingly,

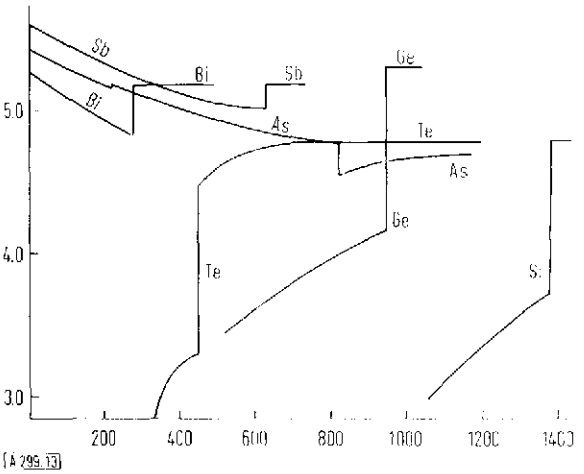

Fig. 13. Dependence on temperature of the "atomic" electrical conductivity of some semimetals in the solid and molten state. The "atomic" conductivity is the product of the specific conductivity and the atomic volume.

Ordinate: Logarithm of the "atomic" conductivity
Abscissa: Temperature [°C]

the jump in conductivity is large and positive for the first three elements mentioned. In spite of their metallic conductivity in the solid state, Bi and Sb are better conductors in the liquid state. For arsenic this holds only at high temperatures, *i.e.* when the transition to a metallic structure is complete.

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German version: Angew. Chem. 75, 508 (1963).

[18] Red phosphorus forms an exception, for on melting, it attains a molecular structure.

[19] Similar phenomena as with semimetals are observed for intermetallic phases. For example, the specific heat of molten InSb reaches a maximum similar to the one exhibited by the specific heat of molten arsenic. Cf. *A. Schneider* and *R. Blachek*, Naturwissenschaften *49*, 465 (1962).

Recent Investigations of Sulfur-Nitrogen Compounds [*]

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The preparation, properties, and structure of cyclic and acyclic sulfur-nitrogen halides are discussed. In the cyclic compounds, S–N rings with localized and delocalized π-bonds occur. In acyclic halides, S–N triple bonds are observed. Organic iminosulfur dihalides are discussed.

Introduction

As a result of numerous investigations begun well over a hundred years ago, various sulfur-nitrogen halides are known (Table 1). Not only do these compounds have remarkable chemical properties, they also raise interesting problems as to chemical bonding. They represent the first examples known so far in pure inorganic chemistry, where single, double, and triple bonds as well as localized and delocalized double bonds in rings occur. Rings with delocalized double bonds may be considered as inorganic aromatic compounds.

[*] Expanded from a plenary lecture given on September 20th, 1961, at the Hauptversammlung der Gesellschaft Deutscher Chemiker at Aachen (Germany).

A starting material that is often used for the preparation of sulfur-nitrogen compounds, including the halides, is the orange-yellow compound tetrasulfur tetranitride S_4N_4, which melts at 178 °C with decomposition. The

Table 1. Inorganic sulfur-nitrogen halides (situation at the end of February 1963).

Fluorides	Chlorides	Bromides
$N_4S_4F_4$	—	
		$(NSBr)_x$
$N_3S_3F_3$	$N_3S_3Cl_3$	
S_4N_3F	S_4N_3Cl	S_4N_3Br
	$SeS_2N_2Cl_5$	—
NSF	NSCl	—
$S_3N_2F_2$	$S_3N_2Cl_2$	—
—	S_3N_2Cl	S_3N_2Br
—	—	$S_2N_3HBr_4$
—	S_3N_3Cl	—
NSF_3	—	—

S_4N_4 molecule is an eight-membered ring (Fig. 1), as is evidenced by electron-diffraction [1] and X-ray structural analyses [2]. One structure proposed that assumed N–N bonds [3,4] was disproved by electron-spin resonance measurements [5].

Two properties of the S_4N_4 molecule are noteworthy:

1. It has only one value for the direct S N distance, *viz.* 1.63 Å, which lies between the value for an S–N single bond (1.74 Å) and that for an S N double bond (1.54 Å).

2. The distance (2.58 Å) between two sulfur atoms not linked by a nitrogen atom is substantially shorter than the sum of the van der Waals radii (3.7 Å), and somewhat longer than an S–S single bond (2.08 Å). Hence there must be some interaction between the sulfur atoms, which led *Lindquist* [6, 7] to assume a p-bond.

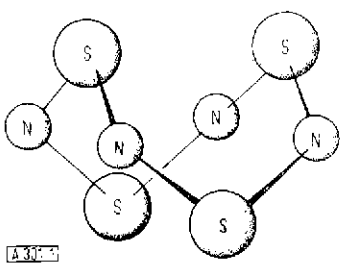


Fig. 1. Structure of tetrasulfur tetranitride, S_4N_4, after *Clark* [2].

The relationship between the S N bond length and the bond order is shown in Table 2. According to Fig. 2, a bond order of 1.5 corresponds to an S–N distance of 1.63 Å [7]. This may be explained most plausibly by a

[1] *C. Lu* and *J. Donohue*, J. Amer. chem. Soc. *66*, 818 (1944).

[2] *D. Clark*, J. chem. Soc. (London) *1952*, 1615; space group $P2_1/m$ (a = 8.75 Å; b = 7.16 Å; c = 8.65 Å; β = 87.5°; Z = 4).

[3] *O. Hassel* and *H. Viervoll*, Tidsskr. Kjemi Bergves. Metallurgi *3*, 7 (1943).

[4] *E. R. Lippincott* and *M. C. Tobin*, J. chem. Physics *21*, 1559 (1953).

[5] *D. Champan* and *A. G. Massey*, Trans. Faraday Soc. *58*, 1291 (1962); *D. Champan, R. M. Golding, A. G. Massey*, and *J. T. Moelwyn-Hughes*, Proc. chem. Soc. (London) *1961*, 377.

[6] *I. Lindquist*, J. inorg. nucl. Chem. *6*, 159 (1958).

π-electron system, which is due to p_π(nitrogen)-d_π(sulfur) overlapping. For such inorganic ring systems and others like them (P N and S N rings), two zero-approximation formulae are conceivable for the electronic

Table 2. Relationship between S–N bond length and S–N bond order (cf. Fig. 2).

Compound	Bond length Å	Bond order	Ref.
NSF_3	1.416	2.7 [*]	[7a, 20]
NSF	1.446	2.5_5	[7a, 20]
$N_4S_4F_4$	1.54	2.0	[21]
$N_4S_4F_4$	1.56	2.0 [*]	[7b]
α-$N_3S_3O_3Cl_3$	1.564	1.9	[24]
$N_3S_3Cl_3$	1.605	1.7	[24]
S_4N_4	1.63	1.5 [*]	[7a]
$N_4S_4F_4$	1.66	1.4	[21]
$N_4S_4H_4$	1.67	1.4	[7b]
NH_2SO_3H	1.73	1.0 [*]	[7b]
NH_2SO_3H	1.74	1.0 [*]	[7c]
SN^+	1.25	3.0 [*]	[7b]
SN	1.496	2.5 [*]	[7c]

[*] These values have been used in Fig. 2.

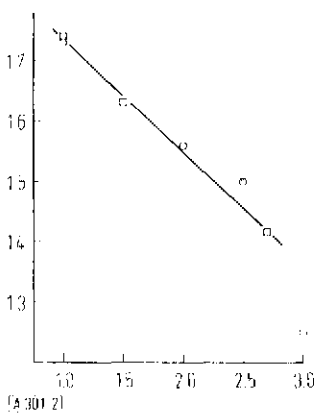


Fig. 2. Relationship between S—N bond length and S–N bond order (cf. Table 1).
Ordinate: Bond length [Å]
Abscissa: Bond order

structures. According to *Craig* [8], the uniform S–N distance can be explained by assuming delocalized π-bonds, such as in benzene. This concept is supported by measurements of the electron-spin resonance of sulfur nitride ions [5]. As an alternative explanation of the bond arrangement in the S_4N_4 rings, *Dewar*, *Lucken*, and *Whitehead* [9] conceive the π-bonds as almost separate three-centered bonds, each involving a central nitrogen atom and two adjacent sulfur atoms; only two electrons are accommodated in each of these three-centered π-bonds. This explanation seems less probable.

[7a] *W. H. Kirchoff*, Ph. D. Thesis, Harvard University, Cambridge, Mass., 1962.

[7b] *D. Chapman* and *T. C. Waddington*, Trans. Faraday Soc. *58*, 1679 (1962). The S–N distance determined for the bond orders 2.5 and 3 cannot be considered in the evaluation.

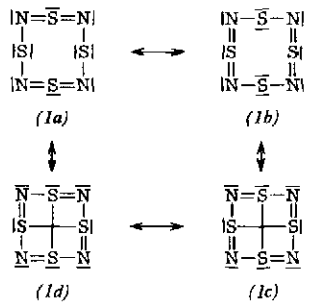
[7c] After *V. Schomaker* and *D. P. Stevenson*, J. Amer. chem. Soc. *63*, 37 (1941).

[8] *D. P. Craig*, Chem. Soc. (London) Spec. Publ. No. 12, 343 (1958); *D. P. Craig* and *N. L. Paddock*, Nature (London) *181*, 1052 (1958); *D. P. Craig*, J. chem. Soc. (London) *1959*, 997.

[9] *M. J. S. Dewar, E. A. C. Lucken*, and *M. A. Whitehead*, J. chem. Soc. (London) *1960*, 2423.

Whereas, according to *Craig* [8], in the case of p_π-p_π overlapping (benzene) the delocalization energy is greatly reduced in non-planar rings, in the case of p_π-d_π overlapping, this effect is less marked because of the greater extension of the d-orbitals. The hybrid at the sulfur atom should be nearly a p^3d hyhrid.

The equivalence of the sulfur atoms that results from the structure of the S_4N_4 molecule was also found by *Faessler* and *Goehring* [10]. In S_4N_4, sulfur has an average oxidation number of +3; formulae *(1a)* to *(1d)* show the most important resonance structures [11].



(1a) *(1b)* *(1d)* *(1c)*

A. Cyclic Sulfur-Nitrogen Halides

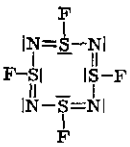
What happens when halogens are allowed to react with S_4N_4? As early as 1880, *Demarçay* [12] who prepared most of the presently known chlorides and bromides of S_4N_4, obtained a yellow chloride of the empirical composititon NSCl by passing chlorine through a suspension of S_4N_4 in chloroform. *Andreacci* [13], as well as *Muthmann* and *Seitter* [14], formulated the chloride as $N_4S_4Cl_4$. Later, on the basis of molecular-weight determinations, *Meuwsen* [15] obtained the correct formula, $N_3S_3Cl_3$. When bromine is allowed to react with S_4N_4 in carbon disulfide, a bronze-colored bromide is formed [16], of which only the composition – NSBr – but not the molecular weight has been determined; this compound is therefore formulated as $(NSBr)_x$. Fluorinated products of nitrogen sulfide have become known only in recent years.

I. Tetrathiazyl Tetrafluoride, $N_4S_4F_4$ [17]

Fluorination of S_4N_4 cannot be accomplished by passing elementary fluorine over solid S_4N_4, since the reaction is too violent and leads directly to sulfur fluorides and nitrogen. Fluorine diluted with nitrogen is also unsuitable, even though the reaction proceeds less violently. The fluorination is best achieved by treating a suspension of S_4N_4 in carbon tetrachloride with silver difluoride. On concentrating the solution, colorless crystals of formula $N_4S_4F_4$ precipitate (m.p. 153 °C, decomposition from 128 °C; density $d_4^{20} = 2.326$ g/cm³; dipole moment $\mu = 0$). $N_4S_4F_4$ is slightly soluble in carbon tetrachloride (3.44 g/l at 20 °C). The compound hydrolyses completely in hot dilute sodium hydroxide solution:

$$N_4S_4F_4 + 12\ H_2O \rightarrow 4\ NH_4F + 4\ H_2SO_3 \qquad (A)$$

From this behavior, it can be concluded that the sulfur in $N_4S_4F_4$ has an average oxidation number of +4, that the fluorine is attached to the sulfur, and that, in agreement with the proposed formula *(2)*, the eight-membered ring of the starting material probably remains stable through the process of fluorination.



(2)

II. Trithiazyl Trifluoride, $N_3S_3F_3$ [18]

The reaction of silver difluoride with $N_3S_3Cl_3$ suspended in carbon tetrachloride produces, colorless crystals of the composition $N_3S_3F_3$ (m.p. 74.2 °C). Even at room temperature $N_3S_3F_3$ is readily volatile. It is very soluble in benzene and carbon tetrachloride. It is stable in dry air, but in moist air it rapidly turns black and decomposes. Dilute sodium hydroxide solution hydrolyses the fluoride quantitatively:

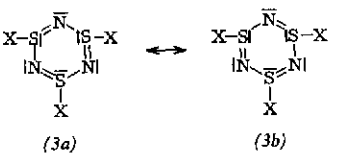
$$N_3S_3F_3 + 9\ H_2O \rightarrow 3\ NH_4F + 3\ H_2SO_3 \qquad (B)$$

This reaction is similar to the hydrolysis of $N_3S_3Cl_3$. In both $N_3S_3F_3$ and $N_3S_3Cl_3$, the sulfur has an average oxidation number of +4; the halogen is attached to the sulfur.

III. Trithiazyl Trichloride, $N_3S_3Cl_3$ [19]

$N_3S_3Cl_3$ is obtained in the form of yellow needles (m.p. 162.5 °C) by passing chlorine into a suspension of S_4N_4 in carbon tetrachloride. The chloride is less sensitive to moisture than the fluoride. It dissolves in benzene, carbon disulfide, and carbon tetrachloride.

While it is assumed that on careful fluorination of S_4N_4 the eight-membered ring remains intact, chlorination of S_4N_4 leads to ring compression. There is experimental evidence that the resonance structures *(3a)* and *(3b)* are the most important ones for the trihalides.



(3a) *(3b)*

[10] *A. Faessler* and *M. Goehring*, Z. Physik *142*, 558 (1955); see also Naturwissenschaften *39*, 169 (1952).

[11] Limiting structures containing sulfur atoms with a residual positive charge can make no important contribution to the total wave function of the molecule because of the short distance between the opposite sulfur atoms and the resulting forces of repulsion.

[12] *E. Demarcay*, C. R. hebd. Séances Acad. Sci. *91*, 854 (1880).

[13] *A. Andreacci*, Z. anorg. allg. Chem. *14*, 246 (1897).

[14] *W. Muthmann* and *E. Seitter*, Ber. dtsch. chem. Ges. *30*, 627 (1897).

[15] *A. Meuwsen*, Ber. dtsch. chem. Ges. *64*, 2311 (1931).

[16] *A. Clever* and *W. Muthmann*, Ber. dtsch. chem. Ges. *29*, 340 (1896).

[17] *O. Glemser*, *H. Schroeder*, and *H. Haeseler*, Naturwissenschaften *42*, 44 (1955); Z. anorg. allg. Chem. *279*, 28 (1955).

[18] *H. Schröder* and *O. Glemser*, Z. anorg. allg. Chem. *298*, 78 (1959).

[19] *A. Meuwsen*, Ber. dtsch. chem. Ges. *64*, 2311 (1931); *H. Schröder* and *O. Glemser*, Z. anorg. allg. Chem. *298*, 78 (1959).

IV. Structural Investigations of $N_4S_4F_4$, $N_3S_3F_3$, and $N_3S_3Cl_3$

Reliable information is available concerning the structures of $N_4S_4F_4$, $N_3S_3F_3$, and $N_3S_3Cl_3$, by which the conclusions based on the chemical evidence were confirmed with the limitation, however, that the fluorides do not form resonance structures.

Measurement of the nuclear magentic resonance of the fluorine [20] gives preliminary data on the structures of $N_4S_4F_4$ and $N_3S_3F_3$. The spectra of both compounds show only one resonance signal, from which it follows that all the fluorine atoms are in structurally equivalent positions, and that the molecules are therefore symmetrical. Furthermore, since the absorption maximum is near that of SF_6 it can be concluded that the fluorine atoms in $N_4S_4F_4$ and in $N_3S_3F_3$ are bound to the sulfur. Finally, the absorption maxima of the fluorine in the two compounds deviate only slightly from each other; therefore, the electron distribution in the fluorine atoms is similar in both cases.

The structure of $N_4S_4F_4$ was elucidated [22] by *Wiegers* and *Vos* [21]. The molecule consists of a puckered eight-membered ring, the form of which is quite different from that of S_4N_4 (Figs. 3a and 3b).

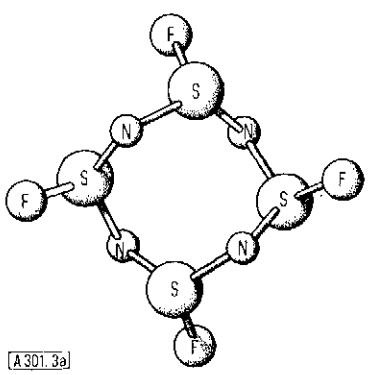


Fig. 3a. Structure of tetrathiazyl tetrafluoride, $N_4S_4F_4$, after *Wiegers* and *Vos* [21]. The $N_4S_4F_4$ ring is projected along the [001] axis.

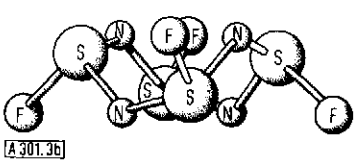


Fig. 3b. Structure of tetrathiazyl tetrafluoride, $N_4S_4F_4$, after *Wiegers* and *Vos* [21]. The $N_4S_4F_4$ ring is projected along the [010] axis.

The fluorine atoms attached to the sulfur atoms are arranged in such a way that a compact molecule is formed [23]. Two different S–N distances, *viz.* 1.66 Å and 1.54 Å [corresponding to a bond order of 1.42 and 2.0, respectively (cf. Table 2)], clearly demonstrate the fact that localized double bonds must be present in $N_4S_4F_4$, and that, accordingly, delocalization of the bonds as in the case of S_4N_4 either does not occur, or occurs only to a slight extent.

In contrast to $N_4S_4F_4$, the $N_3S_3Cl_3$ molecule has only one direct S–N distance, *viz.* 1.605 Å [24,25] (cf. Table 2), which indicates delocalization of the π-bonds and therefore an inorganic aromatic ring. The six-membered ring of the molecule is in the chair form; the nitrogen atoms deviate by an average of 0.18 Å from the plane of the S atoms, and the chlorine atoms pointing into one direction are located in axial positions (Fig. 4).

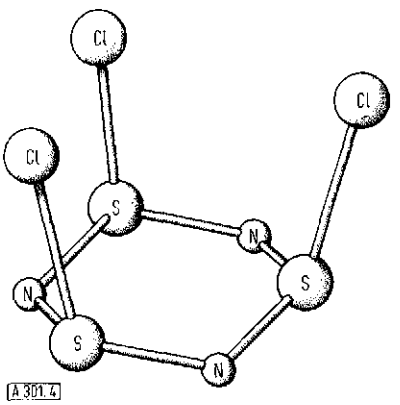


Fig. 4. Structure of trithiazyl trichloride, $N_3S_3F_3$, after *Wiegers* and *Vos* [24].

What type of bond exists in $N_3S_3F_3$? Measurement of the nuclear magnetic resonance showed that all the fluorine atoms are equivalent. However, this is possible only if all the fluorine atoms – like the chlorine atoms in $N_3S_3Cl_3$ – are located in axial positions on one side of the ring. Furthermore, the conclusion that $N_3S_3F_3$, like $N_4S_4F_4$, contains localized double bonds seems justified, since, according to the nuclear magnetic resonance absorption, the electron distribution is very similar in the two compounds.

Why, then, do only localized π-bonds occur in the fluorides, while delocalized bonds are present in the chlorides? Let us consider a fluorine atom linked to a sulfur atom. It polarizes the sulfur, by drawing off electrons, to such an extent that, in comparison to S_4N_4, a weaker repulsion between the lone electron pair on the S and that on the N results. In this way, the bond length can be decreased and the tendency towards formation of a double bond is enhanced. Alternating shorter and longer S–N distances may frequently be more favorable than two proportionately shorter, but equal distances, such as occur in delocalized bonds. That is to say, the attraction term of the bond energy increases exponentially with decreasing distance, so that, in the case of alternating distances, the gain in double bond energy may exceed the delocalisation energy for equal distances. This

[20] *H. Richert* and *O. Glemser*, Z. anorg. allg. Chem. *307*, 328 (1961).

[21] *G. A. Wiegers* and *A. Vos*, Acta crystallogr. *14*, 562 (1961); *16*, 152 (1963).

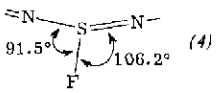
[22] Compare also the preliminary X-ray analysis of $N_4S_4F_4$ by *O. Glemser*, *H. Schröder*, and *H. Haeseler* [17].

[23] $N_4S_4F_4$ crystallizes in the tetragonal form (a = 9.193 Å; c = 4.299 Å; space group $P\bar{4}2_1c$; Z = 2; S–N–S angle = 123.9 °; S–F distance = 1.602 Å; N–S–N– angle = 111.7 °; F–S–N angle = 91.5 °; F–S–N-angle = 106.2 °).

[24] *G. A. Wiegers* and *A. Vos*, Proc. Roy. Soc. (London) *1962*, 387.

[25] Space group $P2_1/m$ or $P2_1$; a = 5.49 Å; b = 11.14 Å; c = 6.05 Å; β = 98.4 °; Z = 2; N–S–N angle = 113.4 °; S–N–S angle = 123.8 °; N–S–Cl angle = 113.8 °; S–Cl distance = 2.150 and 2.084 Å.

effect is intensified by the position of the fluorine, which tends to form an N–S–F angle as wide as possible *(4)*, as is evidenced by the structure of $N_4S_4F_4$ (Figs. 3a and 3b).

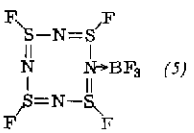


(4)

The same assumptions must be valid for $N_3S_3F_3$. In $N_3S_3Cl_3$, however, the chlorine cannot polarize the sulfur as strongly as fluorine can in $N_3S_3F_3$. Therefore, no preponderance is given localized double bonds and S–N distances are longer, *i.e.* the symmetrical arrangement of chlorine and the gain in delocalizing energy are more favored.

V. Chemical Reactions of $N_4S_4F_4$, $N_3S_3F_3$, and $N_3S_3Cl_3$

$N_4S_4F_4$ can act as a Lewis base adding the Lewis acid BF_3. Gaseous BF_3 and solid, colorless $N_4S_4F_4$ give a green adduct $N_4S_4F_4 \cdot BF_3$ [26], for which the structural formula *(5)* was proposed.


(5)

The substance decomposes after several hours even in a current of dry nitrogen at room temperature.

Gaseous, colorless, unstable NSF is formed by thermal decomposition of $N_4S_4F_4$ [27].

$$N_4S_4F_4 \xrightarrow{300\ ^\circ C/\text{vacuum}} 4\ NSF$$

On heating $N_3S_3Cl_3$, gaseous, pale yellow, unstable NSCl [28] is formed, which readily polymerizes again to $N_3S_3Cl_3$.

$$N_3S_3Cl_3 \xrightarrow[\text{room temp.}]{100\ ^\circ C/\text{vacuum}} 3\ NSCl$$

In order to obtain insight into the course of the hydrolysis of $N_3S_3F_3$, the compound was decomposed with small amounts of water in a glass apparatus. The gaseous compounds, NSF, thionyl imide (HNSO), SO_2, SOF_2, SiF_4, and NH_3 were obtained; their formation may be understood from Scheme 1 [27].

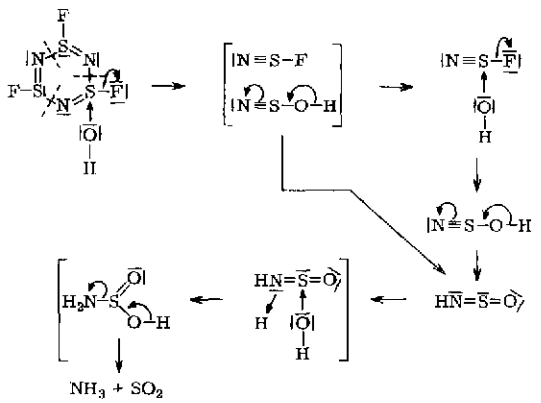
The hydrolysis can be explained as a nucleophilic attack of OH^- on the sulfur. The ring is ruptured, and two fragments, NSF and HNSO, are formed. HNSO may also be formed by further hydrolysis of the NSF, as will be discussed later. Finally, SO_2 and NH_3 are obtained from HNSO, while the appearance of SOF_2 can perhaps be explained by a secondary reaction of NSF with HF and subsequent hydrolysis.

[26] *O. Glemser* and *H. Lüdemann*, Angew. Chem. *70*, 190 (1958).

[27] *O. Glemser* and *H. Perl*, unpublished results.

[28] *O. Glemser* and *H. Perl*, Naturwissenschaften *48*, 620 (1961).

In order to verify this concept of the hydrolysis, other nucleophilic agents were allowed to react with $N_3S_3Cl_3$



Scheme 1. Hydrolysis of trithiazyl trifluoride $N_3S_3F_3$

which is easier to handle than $N_3S_3F_3$ [27]. With potassium cyanide, SCN^- ions were formed, just as expected [29]; with sulfite, $S_2O_3^{2-}$ ions were obtained.

$$N_3S_3Cl_3 + 9\ SO_3^{2-} + 6\ H_2O \rightarrow 3\ NH_4^+ + 3\ S_2O_3^{2-} + 3\ Cl^-$$

On heating in carbon tetrachloride in the presence of pyridine, $N_3S_3Cl_3$ reacts with tetrasulfur tetraimide, $S_4N_4H_4$, to form S_4N_4, *i.e.* it is reduced [30]:

$$4\ N_3S_3Cl_3 + 3\ S_4N_4H_4 \xrightarrow[CCl_4/\text{pyridine}]{\text{heat}} 6\ S_4N_4 + 12\ HCl$$

Assuming $N_3S_3Cl_3$ to depolymerize into 3 NSCl, this process can be conceived as a reaction between NSCl and the hypothetical entity HNS. Heptasulfur imide, S_7NH, behaves similarly to tetrasulfur tetraimide, $S_4N_4H_4$. If the reaction is carried out in the absence of pyridine, which is intended to capture the HCl, a brown-red adduct, $S_4N_4 \cdot 4HCl$ [31], is formed, which reacts with traces of water to give S_4N_3Cl:

$$S_4N_4 \cdot 4HCl \xrightarrow{H_2O} S_4N_3Cl + NH_4Cl + Cl_2$$

VI. Sulfanuric Chloride, $N_3S_3O_3Cl_3$

$N_3S_3O_3Cl_3$ can be obtained from $N_3S_3Cl_3$ through intermediate adducts by oxidation with SO_3 [30]. The compound was first prepared by *Kirsanov* [32] by thermal decomposition of the product formed by the reaction of aminosulfonic acid with PCl_5; he was then able to iso-

[29] *D. A. Skoog* and *J. K. Barlett*, Analytic. Chem. *27*, 369 (1955); *E. Fluck*, *M. Becke-Goehring*, and *R. Dehoust*, Z. anorg. allg. Chem. *312*, 60 (1961).

[29a] According to *A. Meuwsen:* Silicon-Sulfur-Phosphorus Colloquium, I.U.P.A.C., Section Inorganic Chemistry, Münster (Germany) 1954, Verlag Chemie, Weinheim/Bergstr. 1955, careful hydrolysis of $N_3S_3Cl_3$ yields varying amounts of sulfite (65–90%) and thiosulfate (35–18%) while *Schröder* and *Glemser* [18] on rapid hydrolysis observed only sulfite. These conflicting results can now be explained: on careful hydrolysis sulfite is formed and reacts with $N_3S_3Cl_3$ to give thiosulfate. On rapid hydrolysis the latter reaction cannot take place.

[30] *M. Goehring* and *H. Malz*, Z. Naturforsch. *9b*, 567 (1954).

[31] *A. G. MacDiarmid*, Nature (London) *164*, 1131 (1949).

[32] *A. W. Kirsanov*, Doklady Akad. Nauk SSSR, *1950*, 426; Zh. Obshchei Khim. *22*, 88 (1952). According to *Th. Moeller* and *A. Vandi*, AD-274661, 1962 (US-Report). $N_3S_3O_3Cl_3$ is best prepared by the method of *Kirsanov*.

late two colorless isomeric compounds, α-$N_3S_3O_3Cl_3$ (m.p. 144–145 °C) and β-$N_3S_3O_3Cl_3$ (m.p. 42–43 °C).

$$H_2N{-}SO_3H + PCl_5 \rightarrow 3\ HCl + OPCl_3 + ClSO_2{-}N{=}PCl_3 \qquad [33]$$

$$OPCl_3 + (ClSON)_3 \xleftarrow{\text{heat}}$$

According to *Wiegers* and *Vos* [24], the structure of α-$N_3S_3O_3Cl_3$ is closely related to that of $N_3S_3Cl_3$ [34, 34a]. The $N_3S_3O_3Cl_3$ molecule also forms a ring in the chair form; the nitrogen atoms deviate by an average of approximately 0.25 Å from the plane of the S atoms. Again, the ring of sulfanuric chloride has a direct S–N distance of only 1.564 Å, which is considerably shorter than the S–N distance of $N_3S_3Cl_3$ (1.605 Å); cf. Table 2. The chlorine atoms are all located on one side of the molecule in axial positions; the oxygen atoms are in equatorial positions. The S–O bond (length 1.403 Å) has partial double-bond character. In $N_3S_3O_3Cl_3$, delocalized π-bonds are present in the ring. The fact that the S–N distance is shorter than that in $N_3S_3Cl_3$ can be attributed to the fact that the sulfur is polarized by the oxygen and to the fact that the sulfur in sulfanuric chloride no longer has a lone pair of electrons. Figure 5 shows the structure of α-$N_3S_3O_3Cl_3$. S_3O_9, which is isosteric with $N_3S_3O_3Cl_3$, has a similar structure.

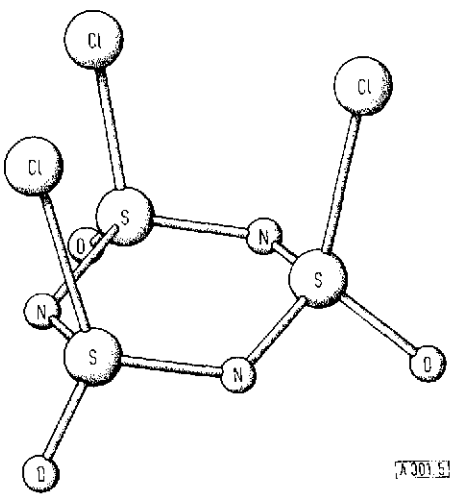


Fig. 5. Structure of sulfanuric chloride, $N_3S_3O_3Cl_3$, after *Wiegers* and *Vos* [24].

VII. Thiotrithiazyl Halides, S_4N_3X

These relatively stable compounds, which are made up of $[S_4N_3]^{\oplus}$ and $X^{\ominus}$ ions, were discoverd by *Demarçay* [12]. S_4N_3Cl, the most thoroughly investigated of the thiotrithiazyl halides, is obtained in the form of bright-yellow crystals [35] by heating S_4N_4 with S_2Cl_2 in the presence of carbon tetrachloride.

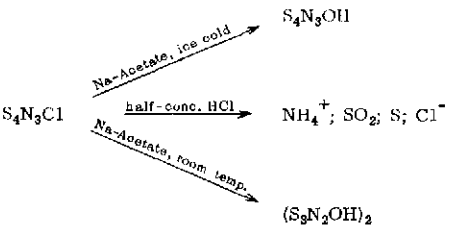
$$3\ S_4N_4 + 2\ S_2Cl_2 \xrightarrow{CCl_4} 4\ S_4N_3Cl$$

It was shown with $^{35}S_2Cl_2$ [36] that the reaction must proceed by way of several intermediates, since, depending on the concentration of the S_2Cl_2, varying amounts of ^{35}S are introduced into the S_4N_3Cl. The S_3N_2Cl mentioned below probably occurs as one intermediate; it is obtained in the cold from S_4N_4 and S_2Cl_2, and decomposes on heating in CCl_4:

$$6\ S_3N_2Cl \rightarrow 4\ S_4N_3Cl + S_2Cl$$

S_4N_3Cl can also be prepared by treating S_4N_4 with $SOCl_2$ [35] or with acetyl chloride [14]. As described above, in the presence of moisture, the adduct $S_4N_4 \cdot 4\ HCl$ is converted into S_4N_3Cl, NH_4Cl, and chlorine. All the other sulfur-nitrogen chlorides known up to the present can also be converted into S_4N_3Cl, *e.g.* $N_3S_3Cl_3$ and $S_3N_2Cl_2$ by heating with S_2Cl_2 in carbon tetrachloride, or S_3N_3Cl by reaction with S_2Cl_2 in the presence of chlorine and carbon tetrachloride.

Thiotrithiazyl chloride is stable in dry air. On heating *in vacuo* to 170 °C, it decomposes with formation of S_4N_4. The compound is insoluble in CCl_4, CS_2, and ether; in many organic solvents, such as $CHCl_3$, benzene, acetic acid, and acetone, it decomposes slowly with development of a red color. S_4N_3Cl is soluble in $SOCl_2$ and anhydrous formic acid. The course of the hydrolysis is dependent on the reaction conditions [37]. With ice-cold sodium acetate solution at 0 °C, the first product formed is black S_4N_3OH, but at room temperature, black $(S_3N_3OH)_2$ is formed. Both hydroxides are unstable, and convert into S_4N_4 after some time. Since the corresponding salts cannot be prepared by reaction of S_4N_3OH with acids, it is unlikely that a structure $[S_4N_4]^+[OH]$ analogous to that of the salts exists. The black hydroxides are probably polymers.



Thiotrithiazyl fluoride, S_4N_3F, is obtained from S_4N_3Cl and HF as moisture-sensitive, yellow-brown crystals of the formula $S_4N_3F \cdot 1.5\ HF$ [38], which decompose if one attempts to remove the hydrogen fluoride. Among the decomposition products, polymeric $(SN)_x$ can be detected [39]. Previously, *Demarçay* [40] prepared the thiotrithiazyl derivatives $[S_4N_3]NO_3$ and $[S_4N_3]HSO_4$ by treating S_4N_3Cl with concentrated nitric and sulfuric acids. Soon afterwards, *Muthmann* and *Seitter* [14] obtained the bromide and the thiocyanate [41]. Orange-

[33] See also *M. Becke-Goehring, T. Mann,* and *H. D. Euler,* Chem. Ber. *94,* 193 (1961).

[34] Space group Pnma or $Pn2_1a$, with a = 7.552 Å; b = 11.540 Å; c = 10.078 Å; Z = 4; N–S–N-angle = 113.0 °; S–N–S-angle = 122.0 °; N–S–Cl-angle = 106.4 °; N–S–O-angle = 111.8 °; O–S–Cl-angle = 107 °.

[34a] See also structural data on α-$N_3S_3O_3Cl_3$ by *A. J. Banneister* and *A. C. Hazell,* Proc. chem. Soc. (London) *1962,* 282.

[35] *A. Meuwsen,* Ber. dtsch. chem. Ges. *65,* 1724 (1932).

[36] *M. Becke-Goehring,* Progr. inorg. Chem. *1,* 207 (1959).

[37] *A. Meuwsen* and *O. Jacob,* Z. anorg. allg. Chem. *263,* 200 (1950).

[38] *O. Glemser* and *E. Wyszomirski,* Chem. Ber. *94,* 1443 (1961).

[39] $(SN)_x$ is described by *M. Goehring* and *D. Voigt,* Naturwissenschaften *40,* 482 (1953); Z. anorg. allg. Chem. *285,* 181 (1956).

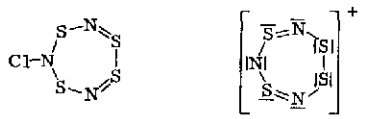
[40] *E. Demarcay,* C. R. hebd. Séances Acad. Sci. *91,* 1066 (1880).

[41] *A. Meuwsen* and *O. Jacob* [37] could not verify the existence of the compound S_4N_3I described by the authors.

yellow $[S_4N_3]Br$ and bronze-colored $[S_4N_3]SCN$ can be precipitated readily from concentrated solutions of S_4N_3Cl in anhydrous formic acid with KBr or NH_4SCN [42,43].

The ready exchange that the chlorine of S_4N_3Cl undergoes with anionic radicals makes a salt-type structure of the thiotrithiazyl halides, such as $[S_4N_3]^+X^-$, probable. This supposition has recently been verified by determination of the molecular weights of the fluoride [38] and chloride [42]: the cation $[S_4N_3]^+$ is monomeric in solution.

Goehring and *Schuster* [44] proposed the structure *(6b)* for the $[S_4N_3]^+$ cation; this corresponds to the formula *(6a)* previously described by *Muthmann* and *Seitter* [14].



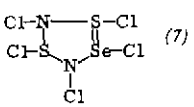
(6a) *(6b)*

Weiss [45] has demonstrated that the $[S_4N_3]^+$ cation is a seven-membered ring by an X-ray investigation of $[S_4N_3]^+NO_3^-$. The investigator leaves the question undecided whether the ring is completely planar. The S–N distances are 1.67 Å on the average, and the S–S distance is 1.94 Å.

Seleniumdithiazyl chloride, $SeS_2N_2Cl_5$ [46] is formed as light-yellow crystals (m.p. 74.3 °C), *i.e.* according to the equation

$$S_4N_4 + Se_2Cl_2 + 4\ SOCl_2 \rightarrow 2\ SeS_2N_2Cl_5 + SO_2 + S$$

Structure *(7)* has been proposed for this compound [47].



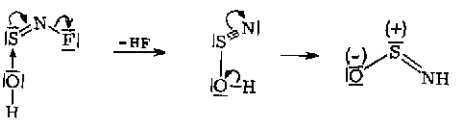
(7)

B. Acyclic Sulfur-Nitrogen Halides

I. Thiazyl Fluoride NSF

NSF is formed in good yield as an unstable, colorless gas with a pungent odor (m.p. −89 °C; b.p. 0.4 ± 2 °C) [49] by fluorination of S_4N_4 with HgF_2 [48]. This fluoride reacts immediately with water forming at first a blue precipitate and – as a gaseous intermediate – monomeric thionyl imide, HNSO [50], the structure of which is now known with certainty [51,52]. The products of the hydrolysis are SO_3^{2-}, F^-, and NH_4^+. On hydrolysis with dilute sodium hydroxide, NSF gives a yellow precipitate as an intermediate, which is again rapidly dissolved. Finally, F^-, SO_3^{2-}, and NH_3 are found, but not in quantitative yield. The course of the reaction has not yet been clarified.

Judging from the products of hydrolysis, and especially from the occurrance of sulfite ions, the starting material must be formulated as $N\equiv S-F$, the sulfur having an oxidation number of +4. However, the following hydrolysis scheme is also conceivable:



The structure of thiazyl fluoride cannot therefore be deduced from its hydrolysis products alone.

Gaseous NSF can be stored without decomposition for some time in a copper vessel at room temperature and pressures below 760 mm Hg. In glass vessels, under the same conditions, decomposition occurs yielding green-yellow crystals of the formula $S_3N_2F_2$ on the walls of the flask (see below). At approximately 200 °C, the reaction with glass occurs rapidly, with formation of S_4N_4, SOF_2, SO_2, SiF_4, and N_2. Since NSF acts as a fluorinating agent, the appearance of SiF_4, SO_2, and SOF_2 is understandable. Chlorination of NSF yields gaseous NSCl, in addition to other products [49]. NSF can be fluorinated with silver difluoride to form NSF_3, whose properties and structure will be described later.

NSF reacts with BF_3 to give colorless crystals [53] which probably represent the adduct $FSN{\cdot}BF_3$. Their exact composition and constitution could not be determined because of their instability. Only at low temperatures do the crystals remain stable for any length of time. After decomposition only a mixture of NSF and BF_3 is present in the gas phase.

The structure of NSF was determined by infrared spectroscopy [20], by measurement of its nuclear magnetic resonance spectrum [20], by electron diffraction [54], and by microwave spectroscopy [7]. The infrared spectrum contains three strong bands, which correspond to

[42] *M. Becke-Goehring* and *H. P. Latscha*, Z. Naturforsch. *17b*, 125 (1962).

[43] Other possible methods of preparation are given by *A. Meuwsen* and *O. Jacob* [37].

[44] *M. Goehring* and *D. Schuster*, Z. anorg. Chem. *271*, 281 (1953).

[45] *J. Weiss*, Angew. Chem. *74*, 216 (1962); Angew. Chem. internat. Edit. *1*, 214 (1962); $[S_4N_3]NO_3$ crystallizes in the monoclinic form; space group $P2_1/c$, with a = 5,81 Å; b = 10.42 Å; and c = 12.47 Å; β = 108 °; Z = 4; see also the other data found for $[S_4N_3]NO_3$ by *R. F. Kruh, A.W. Cordes, R. M. Lawrence*, and *R. G. Goforth*, Acta crystallogr. *14*, 1306 (1961).

[46] *H. Garcia-Fernandez*, C. R. hebd. Séances Acad. Sci. *252*, 411 (1961).

[47] The ring formula is not certain. Structural data for $(SeS_2N_2)Cl_5$ were recently given by *H. Garcia-Fernandez* and *C. Rérat*, C. R. hebd. Séances Acad. Sci. *254*, 1435 (1962). Probable space group: $P2_1/c$, with a = 8.41 Å; b = 17.91 Å; c = 8.16 Å; β = 76 °; Z = 4.

[48] *O. Glemser, H. Meyer*, and *A. Haas*, unpublished data. NSF is also formed by reaction of S_4N_4 with SF_4, and of NH_3 with an excess of SF_4; *O. Glemser* and *S. Austin*, unpublished data.

[49] *O. Glemser* and *H. Richert*, Z. anorg. allg. Chem. *307*, 313 (1961).

[50] *P.W. Schenk*, Ber. dtsch. chem. Ges. *75*, 94 (1942).

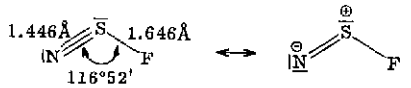
[51] *H. Richert*, Z. anorg. allg. Chem. *309*, 171 (1961).

[52] On hydrolysis of NSF, planar *cis*-HNSO is formed with bond lengths: S–N = 1.511 Å; S–O = 1.456 Å; N–H = 1.004 Å; H–N–S-angle = 117 ° 13′; N–S–O-angle = 120 ° 16′. The possibility of the formation of *trans*-HNSO was not investigated [7a].

[53] *O. Glemser, H. Richert*, and *H. Haeseler*, Angew. Chem. *71*, 524 (1959).

[54] *F. Rogowski*, Z. physik. Chem. *27*, 277 (1961); *O. Glemser, H. Richert*, and *F. Rogowski*, Naturwissenschaften *47*, 94 (1960).

the normal vibrations of a triatomic nonlinear model. However, it was not possible to determine whether the compound should be formulated as NSF or as SNF. Measurement of the nuclear magnetic resonance likewise did not clarify the matter [55]. Interpretation of the electron diffraction led to the formula S=N–F [54], while *Kirchhoff* [7a] deduced from the microwave spectrum that the sulfur, and not the nitrogen, must be the central atom of the molecule, and that therefore it has the formula N≡S–F *(7a)*.



(7a) *(7b)*

This NSF model agrees considerably better with the infrared data than the SNF model does. The SN force constant derived from the infrared spectrum corresponds to a bond order of 2.3 [20,56], and the S–N distance in *(7a)* of 1.446 Å corresponds to a bond order of 2.5 (see Table 2). If the infrared data are used as a basis for the NSF model *(7a)*, then the SN and SF force constants give an S–N distance of 1.47 Å and an S–F distance of 1.64 Å, which agree with the values of *(7a)* [7b]. The mesomeric structure *(7b)* contributes to an SN bond order greater than 2. The formula N≡S–F can be derived from that of SF_4, if the three fluorine atoms are replaced by a triply bound nitrogen atom. The S–N distance in NSF is only slightly greater than that in NSF_3; the S–F distance in NSF is approximately as great as the longer S–F distance in SF_4 (1.646 Å and 1.545 Å, respectively). After NSF_3, NSF has the highest SN bond order of any sulfur-nitrogen compound.

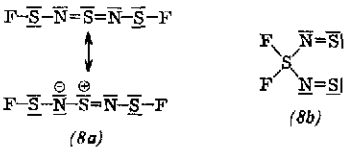
II. Thiazyl Chloride NSCl

The formation of the unstable gas NSCl by thermal decomposition of $N_3S_3Cl_3$ *in vacuo* has already been indicated above [28]. The infrared spectrum of NSCl is similar to that of NSF [49], so that both gases must have similar structures. NSCl has a structural formula analogous to *(7a)* and *(7b)*.

The thionitrosyl halides, SNF and SNCl, which are isomeric with the two thiazyl halides, NSF and NSCl (*i.e.* the sulfur analogues of ONF and ONCl), are still unknown; however, their existence seems likely.

III. Thiodithiazyl Difluoride $S_3N_2F_2$ [57]

When NSF decomposes in a glass flask, green-yellow crystals appear on the walls in low yield (see above); simultaneously, a yellow deposit of S_4N_4 is formed. Sublimation *in vacuo* yields two fractions at 40 °C and 65 °C, respectively. When dissolved in carbon tetrachloride, both fractions give the same absorption in the visible spectral range. Moreover, determinations of their molecular weights and the oxidation number of the sulfur, as well as elemental analysis, yield the same values for both. Probably there are two polymorphous modifications of a single compound of composition $S_3N_2F_2$, for which two structures, *viz. (8a)* and *(8b)*, may be postulated.



(8a) *(8b)*

Formula *(8a)* is given preference, because of the intense color of the fluoride, since resonant structures are possible here, whereas in *(8b)* the bonds are localized.

The surprising fact that NSF polymerizes to $S_3N_2F_2$ is the object of further investigations, which should furnish some clarification of the differing behaviors of NSF and NSCl.

IV. Thiodithiazyl Dichloride $S_3N_2Cl_2$

The chloride, $S_3N_2Cl_2$, with a composition analogous to that of $S_3N_2F_2$ is formed in a completely different way [58]. If trithiazyl trichloride, $N_3S_3Cl_3$, is dissolved in S_2Cl_2 with careful heating, light rust-brown crystals of composition $S_3N_2Cl_2$ precipitate on cooling; however, these are stable for only a short time, even if moisture is excluded. If chlorine is introduced into a suspension of the dichloride in carbon tetrachloride, $N_3S_3Cl_3$ is reformed. The reaction possibly proceeds by way of NSCl according to the equation

$$N_3S_3Cl_3 \xrightarrow{S_2Cl_2/\text{heat}} S_3N_2Cl_2$$

$$3\ S_3N_2Cl_2 + 3\ Cl_2 \rightarrow [6\ NSCl + 3\ SCl_2] \rightarrow 2\ N_3S_3Cl_3$$

Beyond its elemental composition as determined by analysis, no further data on $S_3N_2Cl_2$ are known. It decrepitates with a flash of light on gentle heating and is converted into S_4N_3Cl on heating with S_2Cl_2 in carbon tetrachloride.

V. Further Acyclic Thiazyl Halides

Thiodithiazyl chloride, S_3N_2Cl, forms green crystals and was first obtained by *Demarçay* [12] from S_4N_4 and S_2Cl_2 in the cold; it has been recently reinvestigated by *Becke-Goehring* [59], who found that the reaction

$$S_4N_4 + S_2Cl_2 \rightarrow 2\ S_3N_2Cl$$

must proceed by way of intermediate stages that are still unknown. S_3N_2Cl is also formed when NOCl is allowed to react with S_4N_4, or when $N_3S_3Cl_3$ reacts with NO in nitromethane as solvent [59].

[55] The absorption occurred at +358 ppm.; this value has been confirmed by *Kirchoff* [7]. The reference substance was a saturated KF solution.

[56] *H. Siebert*, Z. anorg. allg. Chem. *273*, 170 (1953).

[57] *O. Glemser* and *E. Wyszomirski*, Angew. Chem. *69*, 534 (1957).

[58] *E. Damarçay*, C. R. hebd. Séances Acad. Sci. *92*, 726 (1881); *A. Meuwsen*, Ber. dtsch. chem. Ges. *65*, 1724 (1932).

[59] *M. Becke-Goehring*, Progr. inorg. Chem. *1*, 221 (1959).

S_3N_2Cl is insoluble in organic solvents. Water causes rapid hydrolysis. The molecular weights of $S_3N_2Cl_2$ and of S_3N_2Cl have not been determined. Perhaps polymeric compounds are involved here. Similar relationships probably exist in the case of the bromide, S_3N_2Br.

When S_4N_4 is refluxed with acetyl bromide, dark-purple monoclinic crystals of $S_2H_3HBr_4$ are formed, which melt sharply at 138 °C [60].

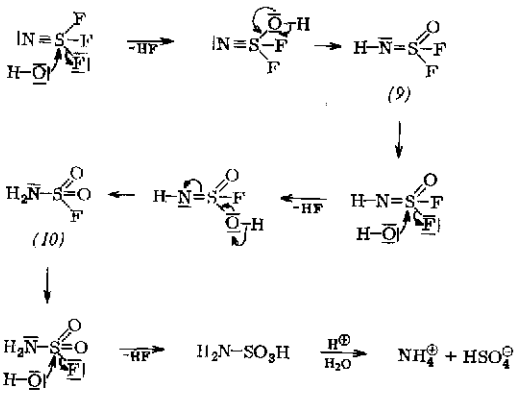
The preparation of the brick-red compound S_3N_3Cl was first described by *Demarçay* [12]. *Meuwsen* was able to reproduce the reaction only once by treating a hot solution of S_4N_4 in chloroform with chlorine. On introduction of additional chlorine, $N_3S_3Cl_3$ crystallized out of the brick-red solution. S_3N_3Cl may therefore be considered as the primary product and $N_3S_3Cl_3$ as the end product of chlorination of S_4N_4. Old literature data on S_2NCl_2 or $S_4N_3Cl_2$ [61] have not yet been confirmed; the existence of these chlorides is doubtful.

VI. Thiazyl Trifluoride NSF_3 [62]

Fluorination of NSF with silver difluoride yields thiazyl trifluoride, NSF_3 (see above). S_4N_4 can be reacted in boiling carbon tetrachloride in such a way that, in addition to NSF, NSF_3 is formed; however, at least ten additional volatile compounds are also produced, including SF_4, SF_6, SOF_2, SO_2, SO_2F_2, and N_2. After distillation in a low-temperature spinning-band column, this complex reaction mixture containing also solid compounds was analyzed by infrared spectroscopy and gas chromatography.

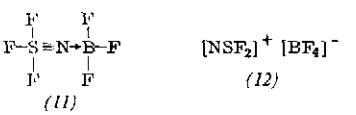
NSF_3 is also formed in addition to NSF when ammonia is introduced into a suspension of sulfur and silver difluoride in carbon tetrachloride; however, the yield is low [63]. Considerable amounts of NSF_3 were reported to form when S_2F_{10} is treated with a deficiency of NH_3. Detailed information is not yet available [63a].

NSF_3 is a colorless gas with a pungent odor (m.p. −72.6 °C; b.p. −27.1 °C). In contrast to NSF, which is extremely unstable, NSF_3 is very stable. In glass vessels, no reaction takes place even at 200 °C. At 500 °C, NSF_3 reacts rapidly with glass, forming SiF_4, SO_2, S, N_2, and metal fluorides [64]. Even at elevated temperatures gaseous hydrogen chloride does not react with NSF_3 and even ammonia gas leaves NSF_3 unaltered at room temperature. NSF_3 is stable to metallic sodium, with which it reacts only on strong heating (approximately 400 °C) to form Na_2S, NaF, and nitrogen. It is also noteworthy that NSF_3 is not attacked by dilute acids. It reacts with water only slowly; decomposition in aqueous solution was attained by boiling with sodium hydroxide solution and subsequent acidification. Sulfamic acid was detected as an intermediate product during hydrolysis. On acidification, it is converted quantitatively into SO_4^{2-} and NH_4^+. The constitution of NSF_3 can be derived from this reaction if it is assumed that the sulfur in the NSF_3, as in sulfamic acid, has the oxidation number +6. Of all the possible classical valence formulae, then, only that with a sulfur-nitrogen triple bond can be considered. With regard to the hydrolysis of NSF_3, Scheme 2 seems to be in accordance with the experimental data.



Scheme 2. Hydrolysis of thiazyl trifluoride, NSF_3.

At the beginning of hydrolysis iminosulfur oxydifluoride, $HNSOF_2$ *(9)*, is formed, the ammonium salt of which has recently been described [65]. The synthesis of $HNSOF_2$ has also recently been carried out [66]. During further hydrolysis of $HNSOF_2$ another proton is transferred to the nitrogen with the formation of iminosulfur dioxyfluoride, H_2NSO_2F *(10)*, which can also be obtained synthetically [67, 68]. Being a Lewis base, NSF_3 reacts with BF_3 to form colorless $NSF_3 \cdot BF_3$ [53], which can be purified by sublimation. According to infrared measurements and molecular-weight determinations, the gas phase consists of a mixture of equivalent amounts of NSF_3 and BF_3. The spectrum of the liquefied compound in the near infrared is not similar to that of the alkali borofluorides. The formula *(11)* is therefore assumed for the liquid state; in the solid state, a fluoroonium compound *(12)* may be present [69].



(11) $\quad$ $[NSF_2]^+ [BF_4]^-$ *(12)*

The instability of $NSF_3 \cdot BF_3$ indicates that the donor activity of the lone electron pair on the nitrogen is considerably weakened by the S–N triple bond.

[60] *R. F. Kruh, A. W. Cordes, R. M. Lawrence,* and *R. G. Goforth,* Acta crystallogr. *14,* 1306 (1961).

[61] *J. M. Fordos* and *A. Gelis,* C. R. hebd. Séances Acad. Sci. *31,* 702 (1850).

[62] *O. Glemser* and *H. Schröder,* Z. anorg. allg. Chem. *284,* 97 (1956); *O. Glemser* and *H. Richert,* ibid. *307,* 313 (1961).

[63] *O. Glemser, E. Wyszomirski,* and *H. Meyer,* unpublished data.

[63a] *B. Cohen* and *A. G. MacDiarmid,* Chem. and Ind. *1962,* 1866.

[64] See also the explanation of this point by *O. Glemser* and *H. Richert* [49].

[65] *F. Seel* and *G. Simon,* Angew. Chem. *72,* 709 (1960).

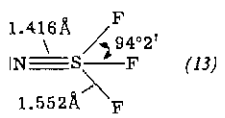
[66] *G. W. Parshall, R. Cramer,* and *R. E. Foster,* Inorg. Chem. *1,* 677 (1962); preparation from NH_3 and SOF_4 in the presence of NaF and ether; cleavage of the etherate with BF_3; b.p. 43 °C.

[67] *H. Jonas* and *D. Voigt,* Angew. Chem. *70,* 572 (1958).

[68] *R. Appel* and *W. Senkpiel,* Angew. Chem. *70,* 572 (1958).

[69] *F. Seel* and *O. Detmer,* Z. anorg. allg. Chem. *301,* 113 (1959).

What structure does this stable NSF_3 have? Measurements of its infrared absorption [20] and of the nuclear magnetic resonance [20] of its fluorine atoms, and interpretation of its microwave spectrum gave a picture that was without contradictions. The nuclear magnetic resonance absorption of NSF_3 lies in the vicinity of the absorption of SF_6, hence all the fluorine atoms must be bound to the sulfur, and must be in equivalent positions [70]. The NSF_3 molecule has therefore C_{3v} symmetry, as can also be inferred from its infrared spectrum. NSF_3 has great similarity to the tetrahedrally coordinated compound OPF_3. The infrared spectra of the two compounds agree with respect to the number and shape of the bands [71]. Calculation of the S–N bond strength from the force constants gives a bond order of 2.7 (*i.e.* approximately 3).These results are confirmed and supplemented by the microwave spectrum [72]. The very short S–N distance of 1.416 Å corresponds to a bond order of approximately 3. For comparison, the S–N distance of the localized double bond in $N_4S_4F_4$ is 1.54 Å. Further structural data are given in formula *(13)*.



(13)

Dipole moment $\mu = 1.91$ Debye

Obviously NSF_3 is a compound that is not only of considerable chemical interest, but is also structurally noteworthy. It is the first substance with an S–N triple bond, and also the first compound in which nitrogen and fluorine together share six covalent bonds with sulfur. NSF_3 can be derived from stable SF_6 by substituting a nitrogen atom for three fluorine atoms. In comparison with SF_6, the F–S–F angle in NSF_3 is increased by only approximately 4 °, and the S–F distance is shortened by approximately 0.01 Å. If the chemical properties are also considered, comparison of NSF_3 and SF_6 seems completely justified. However, while in SF_6 the 3s-, 3p-, and 3d-electrons hybridize to the octahedral state sp^3d^2, in NSF_3, sp^3 hybridization of the orbitals occurs. In addition, two p_π-d_π overlappings take place between the nitrogen and the sulfur. The fact that the F–S–F angle of 94 ° 2′ is less than the ideal tetrahedral angle indicates partial participation of d- and p-states at the sulfur atom. It is interesting to compare the molecules OPF_3 and $FClO_3$, which are isosteric with NSF_3; these also exhibit C_{3v} symmetry.

So far, a fluoride $F-N{=}SF_2$ that is isomeric with thiazyl trifluoride, NSF_3, has not yet been found. Such a fluoride would be a derivative of iminosulfur difluoride, $HN{=}SF_2$, several organic derivatives of which have recently been prepared (see Section C).

C. Organic Imidosulfur Dihalides

The reaction of thionylanilide with PCl_5 to form *phenylimidosulfur dichloride*, $C_6H_5-N{=}SCl_2$, was first described by *Michaelis* [73]. This substance is only stable in solution and cannot be isolated.

According to *W. C. Smith* et al. [74], various types of organic iminosulfur difluorides can be obtained by reaction of SF_4 with compounds containing carbon-nitrogen multiple bonds. For example, fluorides of the type $R-N{=}SF_2$ are formed from SF_4 with organic isocyanates, and fluorides of the type $R-CF_2-N{=}SF_2$ are formed from SF_4 with nitriles.

Trifluoromethylimidosulfur difluoride, $F_3C-N{=}SF_2$ (b.p. −6 °C), is formed from SF_4 and inorganic compounds that have a carbon-nitrogen multiple bond, *e.g.* by heating SF_4 with BrCN, NaCN, NaSCN, $NaSCN/NaF/Cl_2$, cyanuric acid, or inorganic cyanates. The reactions may be formulated as follows:

$$3\ NaCN + 5\ SF_4 \rightarrow 3\ F_3C-N{=}SF_2 + 3\ NaF + S_2F_2$$

$$2\ NaSCN + 3\ SF_4 \rightarrow 2\ F_3C-N{=}SF_2 + NaF + S$$

$$2\ NaSCN + 10\ NaF + 6\ Cl_2 \rightarrow 2\ F_3C-N{=}SF_2 + 12\ NaCl$$

For the formation of *phenyliminosulfur difluoride*, $C_6H_5-N{=}SF_2$ (b.p. 36–36.5 °C/2 mm Hg), by heating phenyl isocyanate with SF_4, it is assumed that the first step consists of an addition of SF_4 onto the carbon-nitrogen bond, followed by a rearrangement *(14)* and subsequent elimination of COF_2:

$$R-N{=}C{=}O + SF_4 \longrightarrow \left[R-N(-C(=O)-F)-SF_3\right] \quad (14)$$

$$\left[R-N(-C(=O)-F)-SF_3\right] \longrightarrow R-N{=}SF_2 + OCF_2$$

α,α-Difluorobenzyliminosulfur difluoride, $C_6H_5-CF_2-N{=}SF_2$ (b.p. 33 °C/2 mm Hg), is formed by heating benzonitrile with SF_4. This reaction, which is common to all nitriles, can be explained similarly to that of phenyl isocyanate *(15)*.

[70] On stronger resolution, the band splits into three bands of approximately equal intensities, with a distance of 54 cycles between the outer bands. This splitting is caused by spin-spin interaction between the nitrogen nucleus and the fluorine nuclei and corresponds to the nuclear moment of the nitrogen. The absorption of the band lies at +187 ppm., as *Kirchoff* [7a] has recently confirmed.

[71] *K. Ramaswamy, K. Sathianandan,* and *F. F. Cleveland,* J. molec. Spectrosc. *9*, 107 (1962), have determined thermodynamic data (heat content, free energy, entropy, and specific heat) for NSF_3 between 100 and 1000 °K.

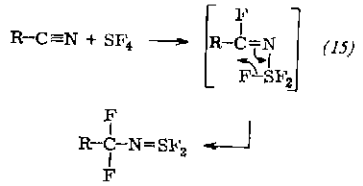
[72] *W. H. Kirchoff* and *E. B. Wilson,* J. Amer. chem. Soc. *84*, 334 (1962).

[73] *A. Michaelis,* Liebigs Ann. Chem. *274*, 201 (1893).

[74] *W. C. Smith, C. W. Tullok, E. L. Muetterties, W. R. Hasek, F. S. Fawcett, V. A. Engelhardt,* and *D. D. Coffman,* J. Amer. chem. Soc. *81*, 3165 (1959); *W. C. Smith, C. W. Tullok, R. D. Smith,* and *V. A. Engelhardt,* ibid. *82*, 551 (1960); *W. C. Smith,* Angew. Chem. *74*, 742 (1962); Angew. Chem. internat. Edit. *1*, 467 (1962).

[75] Formation of the fluoride according to the scheme above is not certain. The first reproducible preparation of S_2F_2 has been reported by *O. Glemser, W. D. Heussner,* and *A. Haas,* Naturwissenschaften *50*, 352 (1963). See also *F. Seel* and *D. Gölitz,* Chimia *17*, 207 (1963).

The same reaction process can be assumed for the fluorination by SF_4 of cyanogen bromide and inorganic cyanides, cyanates, and thiocyanates [76].



(15)

The organic iminosulfur difluorides have remarkable thermal stability. Phenyliminosulfur difluoride is attacked by water and by alcohol, with cleavage of the S–F and S–N bonds. In many reactions, C_6H_5–N=SCl_2 behaves chemically like thionyl chloride; for example, it gives 4,4′-dimethoxydiphenyl sulfide with anisole in the presence of zinc chloride [77]. The reaction of phenyliminosulfur difluoride with lithium aluminum hydride to form aniline is interesting.

Thanks are due to Dr. L. Hofacker for stimulating and informative discussions.

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German version: Angew. Chem. *75*, 697 (1963)

[76] Additional iminosulfur difluorides are reported by *W. C. Smith* et al. [74].

[77] See *F. Loth* and *A. Michaelis*, Ber. dtsch. chem. Ges. *27*, 2540 (1894).

Modern Methods for the Separation and Continuous Measurement in the Gas Phase of Compounds Labelled with Radiocarbon

Radio and Reaction Gas Chromatography [*]

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In biochemical work with isotopic tracers, it is frequently advantageous to investigate samples in the gas phase. In this way, the selectivity of gas-chromatographic separating columns and the sensitivity of detectors can be utilized for both the detection of gas-chromatographic fractions and the determination of their radioactive portions. Conversion of materials separated by gas chromatography into a single standard chemical compound prior to measurement of the radioactivity is recommended. Methods suitable for ^{14}C-labelled compounds can also be applied to those labelled with ^{3}H or ^{35}S.

I. Introduction

Radiochemical detection of a compound is far more sensitive than other methods, since the disintegration of single atoms can be recorded. Under favorable conditions, activities of 10^{-7} to 10^{-9} mC [**] can be measured [1,2].

Good radiochemical detection methods and gas-chromatographic separation methods are of comparable power. Both methods have been highly developed technically, and the constructional elements of their respective detection systems can be readily combined. Gas-chromatographic detectors can be linked to radiation detectors and both worked continuously, so that both the total amount of material and the radioactive portion of fractions leaving a gas-chromatographic column can be measured simultaneously. The conversion of non-volatile compounds into volatile derivatives is, however, a serious problem [3]. It is also possible to carry out reactions with radioactively labelled compounds in a reaction chamber connected to the column inlet and thus to separate the reaction products immediately after they left the reaction chamber [4].

In radio gas chromatography, liquid scintillation counters, ionization chambers, and Geiger-Müller or proportional counting tubes have been employed.

[*] Also Part VI of the series on Reaction Gas Chromatography. Part V: *F. Drawert* and *G. Kupfer*, Hoppe-Seylers Z. physiol. Chem. *329*, 90 (1962).

[**] 1 mC = 3.7×10^{7} disintegrations/sec.

[1] Cf. *H. Götte* in *Houben-Weyl:* Methoden der organischen Chemie. 4th Ed., Thieme, Stuttgart 1955, Vol. III/1, p. 751 et seq.; *G. Herrmann* in *Schwiegk* and *F. Turba:* Künstliche radioaktive Isotope in Physiologie, Diagnostik und Therapie. 2nd Ed., Springer, Heidelberg 1961, pp. 121–304.

[2] *H. Simon* and *F. Berthold*, Atomwirtschaft 7, 498 (1962).

[3] Literature references: *F. Drawert, R. Felgenhauer*, and *G. Kupfer*, Angew. Chem. *72*, 555 (1960).

[4] *F. Drawert:* Gas Chromatography 1962. Butterworth, London 1963, p. 347, where further references are given.

II. Radiation Detectors

1. Liquid Scintillation Counters [5]

If radioactive gas-chromatographic fractions are collected in a solution of a scintillator (diphenyloxazole in toluene), the combination provides an important method for the continuous measurement of ^{14}C. The carrier gas drives the scintillation fluid in a circulatory system past a photomultiplier and increases in radioactivity are integrally indicated [6]. In another technique, the fractions are collected in silicone oil in a fraction collector and are measured discontinuously, using anthracene as scintillator [7]. Plastic helices with imbedded scintillator have also been used for the continuous flow measurement of ^{14}C-labelled compounds [8].

Evans and *Willard* [9] lead the gas-chromatographic fractions past a crystal scintillator (detection of 10^{-13} g of $CH_3{}^{82}Br$ and 10^{-15} g of $CH_3{}^{80}Br$). *Herr* et al. [10] put ampoules of radiation products into an ampoule-breaker (gas-chromatographic insertion accessory) and led the fractions through a glass helix to a solid scintillator (an NaI(Tl) crystal). Radiation products of benzene [11] and other β-emitters [12] have also been measured by the scintillation method after separation by gas chromatography.

Transference from the gaseous to the liquid phase is not absolutely necessary, since numerous very sensitive methods for measuring ^{14}C in the gas phase are available.

2. Ionization Chambers

Various types of continuous-flow ionization chambers for use with gas chromatography have been described. *Cacace* [13] described a method in which the effluent gas is mixed with additional carrier gas after passing through the katharometer cell (gas-chromatographic detector) and before entering the ionization chamber. In this arrangement, it is possible to maintain a constant flux through the ionization chamber (10 l/hr; chamber volume: 100 ml) independent of column conditions. A high rate of gas flow prevents condensation of compounds with boiling points up to 155 °C. The minimum detectable activity is about 2×10^{-4} μC. Various heatable chambers have been described for measuring the radionuclides ^3H, ^{14}C, and ^{35}S [13–16]. Improved results are obtained if the fractions separated by gas chromatography are either ignited to CO_2 at 650 °C [17] or converted into methane and hydrogen by treatment with zinc and nickel oxide at 650 °C [18] before passing through the ionization chamber.

Continuous-flow ionization chambers are predominantly provided with oscillating capacitor type amplifiers whose sensitivity is very dependent on the input resistance. Sensitivities of from ca. 10^{-2} μC are reported for ^{14}C and ^3H. [15, 16]. The background effects of ionization chambers are somewhat high and cannot be reduced efficiently [2]. Heating the chamber alters the background unfavorably and often causes base-line drift. One advantage of the ionization chamber is that relatively high activities (0.1 to 1.0 mC) can be measured without difficulty.

3. Geiger-Müller and Proportional Counting Tubes

In recent years, Geiger-Müller and particularly proportional counting tubes have been introduced for the measurement of weak β-rays. Both types are applied as continuous-flow counting tubes in combination with gas chromatography.

Emmett et al. [19] studied the behavior of [^{14}C]-ethylene and unlabelled propylene toward catalysts (micro-reaction chamber connected to the column) by separating the products by gas chromatography and measuring their radioactivity with a continuous-flow Geiger-Müller counting tube [20]. *Cacace* et al. [21] separated the acids produced by irradiation of mixtures of pentane and $^{14}CO_2$ by gas chromatography and oxidized the fractions to CO_2, which was then converted into barium carbonate for counting with a stationary Geiger counter. *Yanovskii* et al. [22] employed a counter provided with a thin mica window. *James* used continuous-flow tubes [23] or a continuous-flow proportional counting tube [24] made of copper and brass with polyethylene insulators and with a tungsten counting wire as anode and determined the radioactivity of gas-chromatographic fractions after ignition to CO_2.

Extensive investigations of continuous-flow proportional counters have been published by *Wolfgang* and *Rowland* [25]; metal counting tubes gave good results using helium/methane mixtures. Precise working conditions (plateau; counting and carrier gas; resolving power; interferences) are reported for internally silvered glass counting tubes (volumes: 10, 20, and 85 ml) fitted with a tungsten counting wire [26]. For γ-rays, *Herr* et al. [10]

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[5] *E. Rapkin*, Atomwirtschaft *7*, 508 (1962).

[6] *G. Popjak, A. E. Lowe, D. Moore, L. Brown*, and *F. A. Smith*, J. Lipid. Res. *1*, 29 (1959); Chem. Abstr. *54*, 10409 (1960); cf. *A. E. Lowe* and *D. Moore*, Nature (London) *182*, 133 (1958).

[7] *A. Karmen* and *H. R.Tritch*, Nature (London) *186*, 150 (1960).

[8] *B. L. Funt* and *A. Hetherington*, Science (Washington) *129*, 1429 (1959).

[9] *J. B. Evans* and *I. E.Willard*, J. Amer. chem. Soc. *78*, 2908 (1956).

[10] *W. Herr, F. Schmidt*, and *G. Stöcklin*, Z. analyt. Chem. *170*, 301 (1959).

[11] *R. M. Lemmon, F. Mazzetti, F. L. Reynolds*, and *M. Calvin*, J. Amer. chem. Soc. *78*, 6414 (1956).

[12] *A. A. Cordus* and *I. E.Willard*, J. Amer. chem. Soc. *79*, 4609 (1957).

[13] *F. Cacace* and *I. Ul Haq*, Science (Washington) *131*, 732 (1960).

[14] *L. H. Mason, H. J. Dutton*, and *L. R. Bair*, J. Chromatogr. *2*, 322 (1959).

[15] *H. E. Dobbs*, J. Chromatogr. *5*, 32 (1961).

[16] *H.W. Scharpenseel*, Angew. Chem. *73*, 615 (1961).

[17] *F. Cacace, A. Guerino*, and *I. Ul Haq*, Ann. Chimica *50*, 915 (1960); Chem. Abstr. *55*, 3269 (1961).

[18] *F. Cacace*, Ann. Chimica *50*, 931 (1960); Chem. Abstr. *55*, 4338 (1961); *F. Cacace* and *G. Ciranni*, Atti Accad. naz. Lincei, Rend., Cl. Sci. fisiche, mat. natur. *28*, 865 (1960); Chem. Abstr. *55*, 1342 (1961).

[19] *R. I. Kokes, H.Tobin*, and *P. H. Emmett*, J. Amer. chem. Soc. *77*, 5860 (1955).

[20] *I.T. Kummer*, Nucleonics *3*, 27 (1948).

[21] *B. Aliprandi* and *F. Cacace*, Gazz. chim. ital. *89*, 2268 (1959); Chem. Abstr. *55*, 6364i (1961).

[22] *M. I.Yanovskii, D. S. Kapustin*, and *V. A. Nogotkov-Ryutin*, Dokl. Akad. Nauk USSR *9*, 391 (1956); Chem. Abstr. *53*, 7719b (1959).

[23] *A.T. James* in *D. Glick:* Methods of Biochemical Analysis. Interscience, New York 1960, Vol. 8, p. 1.

[24] *A.T. James* and *E. A. Piper*, J. Chromatogr. *5*, 265 (1961).

[25] *R.Wolfgang* and *F. S. Rowland*, Analytic. Chem. *30*, 903 (1958).

[26] *I. K. Lee, E. K. C. Lee, B. Musgrave, Yi-Noo Tang, I.W. Root*, and *F. S. Rowland*, Analytic. Chem. *34*, 741 (1962).

used a continuous-flow counting tube provided with a capillary flow tube in its counting chamber, or a continuous-flow proportional counting tube made of stainless steel with teflon insulators and a tungsten counting wire of 0.05 mm diameter; the latter tube showed a back ground effect of 40 impulses/min at 210 °C [27]. *Lieser* et al. [28] fitted a continuous-flow proportional counting tube (glass tube with fused-in stainless-steel cathode and a tungsten counting wire of 26 μ diameter) into the thermostat of a gas chromatograph.

III. Methods of Measurement

Precise measurement of weak β-rays demands that all samples be in the same chemical form. If the radioactivity of gas-chromatographic fractions is measured in a counting tube without preliminary conversion into a common chemical compound, the count obtained depends on both the quantity and composition of the material [26]. According to *Simon* [2], there is no counting method available by which any and every ^{14}C-labelled compound can be determined as such with good sensitivity and reproducibility. We therefore converted gas-chromatographic fractions either into CO_2 by ignition according to the methods of *James* [24] and *Cacace* [17], or into methane as previously described by *Zlatkis* [29] before measurement of their radioactivity. In this way, there is no need to correct the results obtained since the measurement of a variety of radioactive compounds with different counting efficiencies is not involved [26].

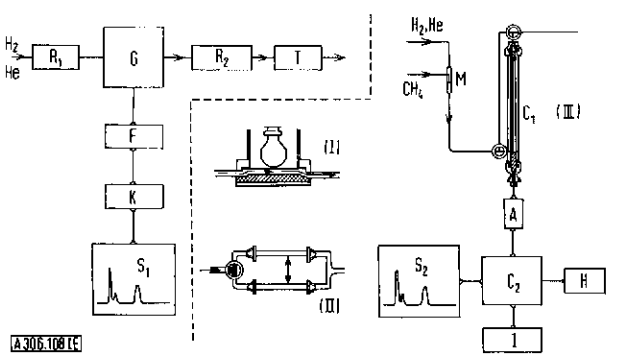

Fig. 1. Block diagram for radio-gaschromatographic arrangements.
G = Gas chromatograph; F = Bridge current unit (Siemens and Halske, Karlsruhe); K = Katharometer (Siemens); S_1 = Compensating linear recorder (Kompensograph, Siemens); R_1, R_2 = Reaction chambers; T = Drying tube.

Measuring arrangement:
I = End-window continuous-flow cuvette (see Fig. 2).
II = Absorption of $^{14}CO_2$ after combustion of gas-chromatographic fractions.
III = Continuous-flow proportional counting tube (see Fig. 3).
C_1 = Counting tube; M = Mixing cell; A = Pre-amplifier (FH 524); C_2 = Counting apparatus (scaler FH 49); H = High voltage source, 5 kV (FH 505); I = Impulse timer (FH 449); S_2 = Potentiometric recorder (FH 585).
FH indicates apparatus manufacturd by Frieseke and Hoepfner, Erlangen-Bruck (Germany).

As shown in Fig. 5 (see below), the plateau length, and hence the counting efficiency, is constant for mixtures containing 20–40 % methane and 80–60 % hydrogen.

Conversion of gas-chromatographic fractions into a common compound also makes it superfluous to heat the counting tube. Even with heated tubes, a certain amount of condensation and hence of contamination of the counting tube is unavoidable. Raising the operating temperature gives rise to plateau shifts with simultaneous flattening of the plateau and increase in the background effect. Moreover, counting tubes are not indifferent to the passage of inactive compounds which often give rise to pseudosignals and uncontrollable side effects.

For several reasons hydrogen is used most frequently as carrier gas. In combination with a continuous-flow proportional counting tube, the most frequently used carrier and counting gases have been argon [24], helium [26,27], rare gases mixed with methane or propane, and methane [28] or propane alone. *Lieser* et al. [28] found no plateau when using argon or hydrogen as counting gas. We have concentrated on measurements using hydrogen as carrier gas with admixture of methane or propane as counting gas. The various experimental arrangements are shown in Fig. 1.

1. Experimental Arrangement I

For exploratory measurements, combination of a continuous-flow cuvette with a methane continuous-flow counter (Fig. 2) proved useful. The cuvette is separated from the counting chamber by a thin window, so that as a result of the spatial separation of carrier and counting gas, the results measured are relatively independent of the nature of the carrier gas. The cuvette (Fig. 2) is constructed in such a way that its base can be moderately heated. In order to obtain a favorable counting geometry, two windows on opposite walls of the cuvette may be used. The relation between the volume of a radioactive standard gas and the measured number of impulses is linear. Experimental arrangement I is particularly advantageous for respiration and assimilation studies with ^{14}C-labelled gases.

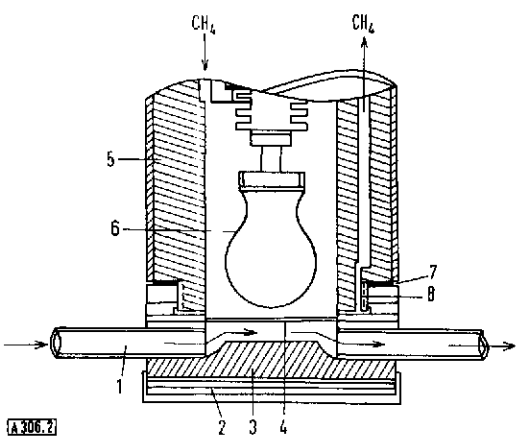

Fig. 2. End-window continuous-flow cuvette and continuous-flow methane counter (FH 407) in combination with scaler FH 49.
1 = Inlet tube connection (Ermeto tubing, 8 mm external diameter, 1 mm wall thickness); 2 = Base plate; 3 = Flow guide; 4 = End-window (gilded Hostaphan foil, surface coverage ca. 0.8 mg/cm²); 5 = Cathode; 6 = Counting wire loop (anode); 7 = Gasket; 8 = Screw closure (flow control).

[27] *H. I. Ache, A.Thiemann*, and *W. Herr*, Z. analyt. Chem. *181*, 551 (1961).

[28] *K. H. Lieser, H. Elias*, and *F. Sorg*, Z. analyt. Chem. *191*, 104 (1962).

[29] *A. Zlatkis* and *J. A. Ridgway*, Nature (London) *182*, 130 (1958).

2. Experimental Arrangement II

This arrangement permits discontinuous measurement of $^{14}CO_2$.

A furnace, charged with copper oxide (R_2 in Fig. 1), is attached to the outlet of the gas chromatograph [30]. The ignition tube (quartz) is joined to the metallic outlet of the gas chromatograph and to the water-absorption tube (T in Fig. 1; magnesium perchlorate) by short connections of silicone rubber tubing. Each individual substance revealed by the detector of the gas chromatograph can be collected after combustion using an absorption tube filled with soda-lime. The soda-lime tubes are easily interchangeable. The hold-up time of a substance between the detector and the diversion cock depends on the volume of the tube connections and on the rate of gas flow; this can be determined by means of a radiation detector. The soda-lime is decomposed with 89 % phosphoric acid in a glass apparatus [2,31,32] provided with a two-armed vessel [1], and the $^{14}CO_2$ in the gas phase determined.

3. Experimental Arrangement III

A continuous-flow proportional counting tube was tried out for continuous measurements, especially with hydrogen as carrier gas. Proportional counting tubes have the advantage over Geiger-Müller tubes of much shorter recovery times, with consequent reduction in coincidence losses at high counting rates, and the ability to detect primary electrons of differing ionizing power. Furthermore, they generally have good, relatively long plateaux [2,33–36] and are comparatively simple to set up. This also applies to a counting tube we built ourselves following the constructional details given by *Curran* [37].

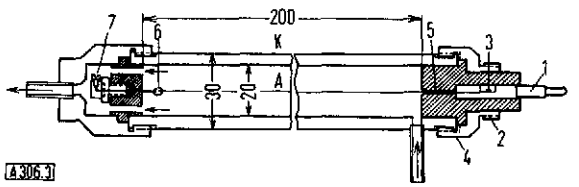

Fig. 3. Continuous-flow proportional counting tube.
A = Anode (counting wire); K = Cathode (counting tube wall); 1 = Plug for pre-amplifier; 2 = Screw thread for adaptor connection for pre-amplifier; 3 = Counting wire anchor (soldered); 4 = End-cap; 5 = Passage for counting-wire through the Teflon insulator; 6 = Glass bead; 7 = Counting-wire tension adjuster. All dimensions in mm.

The cathode is a brass cylinder with an internal diamater of 20 mm. The inner surface was finely ground, polished, and occasionally gilded. As counting wire we used a platinum-iridium wire [*] soldered onto a brass pin *(1)* which was passed centrally through an insulator plug of teflon by means of a glass capillary *(5)* and fixed to a glass bead *(6)* close to a second teflon insulator at the opposite end of the tube. The glass bead prevents distortion of the electric field. A thicker platinum wire (0.4 mm in diameter) is fused into the glass bead, passes centrally through the second teflon insulator, and is attached to a tightening device *(7)*. The direction of gas flow is shown by arrows in Figure 3. Three-way stopcocks are provided at the inlet and outlet to allow for both continuous or stationary measurements. The brass pin soldered to the counting wire is connected with the pre-amplifier. In order to minimize the background effect, the counting tube is maintained in the vertical position and is covered by a lead shield (wall thickness: 3–10 mm). The background effect depends on the carrier gas and the quantity of methane mixed with it. Characteristics and working data are obtained using a standard radiation source [**] or with a standard gas ($^{14}CO_2/CO_2$).

Using hydrogen as carrier gas and (with admixture of about 10 % of methane) as counting gas, the background effect of the counting tube lies under 100 impulses/min and becomes less with increasing additions of methane (3.6 kV; test source). Under the same conditions, the counting rate [38] is substantially constant for methane contents of more than 30 %. The plateau curves

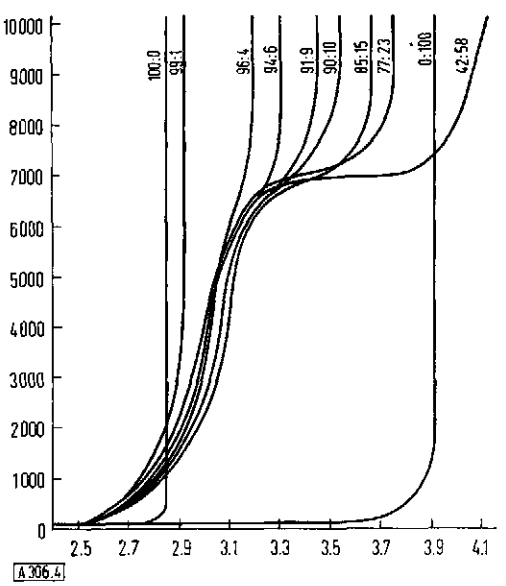

Fig. 4. Plateau curve obtained for the continuous-flow proportional counting tube shown in Figure 3 with a test source. The numbers on the curves indicate the proportions of hydrogen/methane in the mixture (v/v).
Ordinates: Counting rate [counts/min]
Abscissae: Counting wire potential [kV]

for selected hydrogen/methane mixtures, measured using a constant radiation source (standard source) are shown in Figure 4. A plot of different hydrogen/methane ratios in the gas mixture against the plateau length (Fig. 5) shows the optimum ratio. In the optimum range (80–60 % H_2; 20–40 % CH_4), there is a certain buffer action against variation of the gas composition.

The geometry of the counting tube (internal volume, 62.8 ml) ensures a relatively long retention time for the gases in the counting chamber. The flushing time is short

[30] *F. Pregl* and *H. Roth:* Quantitative organische Mikroanalyse. 7th Ed., Springer, Vienna 1958.

[31] *H. Simon, H. Daniel,* and *J. F. Klebe,* Angew. Chem. *71*, 303 (1959).

[32] *F. Drawert* and *O. Bachmann,* unpublished data.

[33] *K. H. Schweer* and *E. Uhlmann,* Atompraxis *7*, 453 (1961).

[34] *R. F. Glascock:* Isotopic Gas Analysis for Biochemists. Academic Press, New York 1954; Atomics *6*, 329 (1955).

[35] *W. Bernstein* and *R. Ballentine,* Rev. Sci. Instruments *21*, 158 (1950).

[36] *H. Klenitz* and *D. Riedel,* Z. analyt. Chem. *179*, 93 (1961).

[37] *S. C. Curran* in *S. Flügge:* Handbuch der Physik. Springer, Heidelberg 1958, Vol. 45, p. 174.

[*] Platinum-iridium (90:10) wire with a very constant diameter of 0.08 mm from Heraeus, Hanau (Germany).

[**] ^{137}Cs, 25 μC (5 mr/h).

[38] The counting rate is the number of impulses per minute. Cf. *Friedländer* and *Kennedy:* Lehrbuch der Kern- und Radiochemie. Thiemig, München 1962, p. 218 et seq.

enough to ensure that sharp activity-maxima are recorded. The general detection limits for ^{14}C are from 5×10^{-4} to 2×10^{-4} μC (using propane as counting gas: 2×10^{-5} μC).

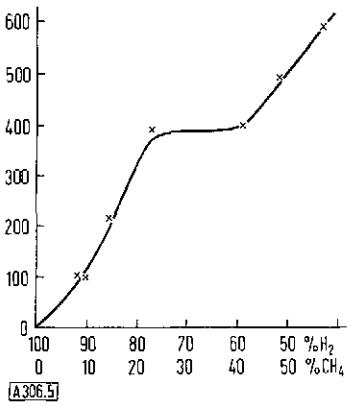

Fig. 5. Optimum operating conditions for the counting tube shown in Figure 3.
Ordinate: Plateau length [V]
Abscissae: Composition of the counting gas

We used two procedures to convert the gas-chromatographic fractions into a common chemical compound: a) Combustion of the organic material to CO_2 and H_2O in a flow of helium over CuO at 700 °C (Pregl-Roth furnace as used for N analysis [30]; R_2 in Fig. 1). The water-absorption tube was packed with coarse $Mg(ClO_4)_2$ and was 10–20 cm long and 0.6 cm in diameter.

b) Cracking of the organic material at 420 °C in a flow of hydrogen over Raney-nickel [39]. The metal cracking-tube was 10 mm in external and 8 mm in internal diameter, and was 20 cm long (R_2 in Fig. 1).

IV. Applications of Radio and Reaction Gas Chromatography

1. Using experimental arrangement I, preliminary investigations were made of the ^{14}C-labelled alcohols arising from fermentations in the presence of added [^{14}C]-glutamic acid. The alcohols were extracted with ether/pentane (70:30), converted into olefins [3,40–42], and then separated by gas chromatography. The distribution of radioactivity among the individual alcohols produced during the fermentation was then determined more accurately using experimental arrangement II. The alcohols were concentrated by extraction with ethyl chloride and separated by gas chromatography; the fractions were ignited, and the CO_2 was absorbed in soda-lime. Figure 6 shows the distribution of radioactivity.

2. In order to analyse fatty acids by gas chromatography, these were converted into their methyl esters by treatment with boron trifluoride and methanol [43,44]. The method was tested using [^{14}C]-acetic acid to see how much esterification already occurs at room temperature.

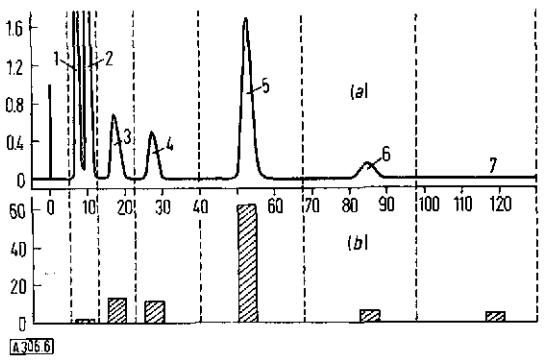

Fig. 6. Radio-gaschromatographic analysis of ^{14}C-labelled compounds from a yeast fermentation containing [^{14}C]-glutamic acid.
a) Gas chromatogram; b) Radiogram.
1 = Ethyl chloride; 2 = Low-boiling fraction (esters, aldehydes, methanol); 3 = Ethanol/isopropanol; 4 = Isobutanol; 5 = Isoamyl alcohol; 6 = n-Amyl acetate; 7 = High-boiling fraction.
The dotted lines indicate where the soda-lime CO_2-absorption tubes were exchanged.
Separation column: 5.80 m Ermeto tube (8 mm external diameter, 1 mm wall thickness); Packing: dinonyl phthalate/sterchamol (20 + 100); connected to an 80 cm tube packed with ethyl D-tartrate/kieselguhr (65 mesh) (20 + 100); 80 °C; 50 ml of He/min; Radiation detector: 85 ml gas-filled counting tube (Berthold, Wildbad (Germany)) combined with apparatus similar to Fig. 1.
Ordinates: a) Recorder potential [mV]
b) Activity [% of total activity]
Abscissae: Time [min]

For this aim, acetic acid was liberated from sodium [^{14}C]-acetate by treatment with 89 % phosphoric acid, and an excess of boron trifluoride/methanol was added. The esterification mixture was then either passed through a heated reaction vessel (a brass tube 10 cm long and 8 mm in diameter) or passed directly into the separation column. It was found that esterification was complete only when the reaction chamber was heated at 180 °C.

3. Saponification of $K^{14}CN$ to [^{14}C]-formate [45] was investigated to determine whether the reaction goes to completion and whether there are volatile by-products. Investigation of the formic acid liberated or of its methyl ester (BF_3/CH_3OH) by gas chromatography and radiochemistry showed that the formic acid is formed in satisfactory purity.

4. In order to study transesterification, the following experiment was carried out: 10 ml of methyl propionate, 10 ml of ethyl propionate, 0.2 ml of 98 % phosphoric acid, and 0.94 mg of sodium [^{14}C]-acetate [46] were refluxed for 30 min. Samples of the mixture were sub-

[39] The catalyst was prepared from Raney-alloy (50% Al, 50% Ni) from Messrs. Schuchardt, München (Germany). Cf. *K. Wimmer* in *Houben-Weyl:* Methoden der Organischen Chemie. 4th Ed., Thieme, Stuttgart 1955, Vol. IV/2, p. 173.

[40] *F. Drawert*, Vitis, Ber. Rebenforsch. *2*, 172 (1960).

[41] *F. Drawert* and *K. H. Reuther*, Chem. Ber. *93*, 3066 (1960).

[42] *F. Drawert* and *G. Kupfer*, Hoppe-Seylers Z. physiol. Chem. *329*, 90 (1962).

[43] *F. Drawert, H. J. Kuhn*, and *A. Rapp*, Hoppe-Seylers Z. physiol. Chem. *329*, 84 (1962).

[44] *L. D. Metcalfe* and *A. A. Schmitz*, Analytic. Chem. *33*, 363 (1961).

[45] *D. G. Grant* and *H. S. Turner*, Nature (London) *165*, 153 (1950). We prepared $K^{14}CN$ in 0.1% aqueous solution in a sealed tube; cf. *A. Murray* and *D. L. Williams:* Organic Syntheses with Isotopes. Interscience, New York 1958, Part I, p. 31.

[46] Sodium [^{14}C]-acetate (27.6 μC/mg) was supplied by the Isotopenlaboratorium, Kernforschungszentrum Karlsruhe (Germany).

mitted to gas chromatography, the separated fractions were cracked to methane, and their radioactivity was measured in a continuous-flow proportional counting tube. Propionates were shown to transesterify with the labelled acetic acid (Fig. 7).

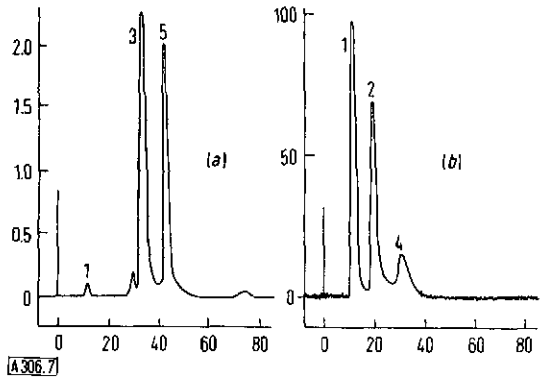

Fig. 7. Transesterification of esters of propionic acid with [^{14}C]-acetic acid.
a) Gas chromatogram; b) Radiogram; 1 = Methyl acetate; 2 = Ethyl acetate; 3 = Methyl propionate; 4 = Propyl acetate; 5 = Ethyl propionate. Column: 5.20 m long, Packing: Polywax 2000/Kieselguhr (65 mesh) (20 + 100); 80 °C; 52 ml of H_2/min. Radiation detector: Arrangement III; 17.4 ml of CH_4/min; H_2:CH_4 = 3:1; 3.6 kV.
Ordinates: Recorder potential [mV]
Abscissae: Time [min]

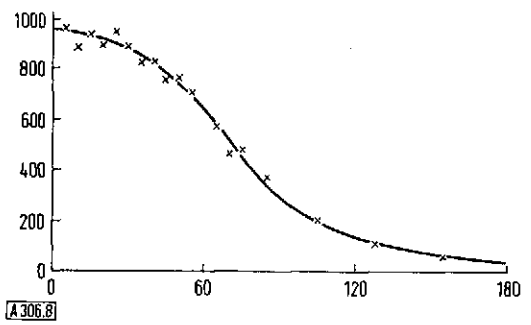

Fig. 8. Course of assimilation of $^{14}CO_2$ (initial concentration 0.913 μC/ml of CO_2) by a vine in a closed chamber. The gas mixture was initially 13.7 l of air and 20 ml of CO_2.
Ordinate: $^{14}CO_2$ remaining in the reaction chamber [counts/min/ml]
Abscissa: Time [min]

5. The $^{14}CO_2$ assimilation of a vine was investigated using experimental arrangement III without reaction units. Gas samples were removed from the closed experimental chamber after equal time intervals and analysed by gas chromatography (Fig. 8).

6. The efficiency of hydrogenation catalysts at different temperatures can be investigated by hydrogenating over the catalyst in a reaction tube, separating the products by gas chromatography, and determining their radioactivities after cracking to methane [4].

Summary

Our investigations show that results of good reproducibility are obtained using hydrogen with methane or helium with methane as carrier and as counting gases, if the fractions separated by gas chromatography are converted into either methane or CO_2 prior to radiometry. Increases in the sensitivity and precision of radiometry in the gas phase effected corresponding reductions in the amounts of labelled material required. Apart from the often considerable savings in the costs of materials, the radiation level in biological investigations is reduced. Complete destruction of the analysed material can be avoided by applying stream splitting and measurement of the radioactivity in parallel.

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COMMUNICATIONS

Interaction of Triphenylmethyl Salts and Quaternary Cycloimmomium Salts with Pyridine and Aromatic and Aliphatic Amines

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Dedicated to Prof. Dr. F. Kröhnke on the occasion of his 60. birthday

Compounds of the n-electron-donor type (D), *e.g.* pyridine, add onto the triphenylmethyl cation ($Tr^{\oplus}$), which is formed from triphenylmethyl halides in solvents of high dielectric constant without pronounced n-donor properties [1], and thus bring about the disappearance of the characteristic visible absorption bands (halochromic bands) at 435 and 415 mμ [2].

$$Tr{-}X + D \rightleftharpoons Tr^{\oplus}\cdots X^{\ominus} + D \overset{k_1}{\rightleftharpoons} TrD^{\oplus}\cdots X^{\ominus}$$

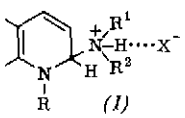
These processes are reversible equilibria that are dependent on the concentration and solvent, as has been shown by means of spectroscopic and conductivity measurements with triphenylmethyl bromide [2]. The association constant K_1 for $TrD^{\oplus}\cdots X^{\ominus}$ in 1,1,2,2-tetrachloroethane at 20 °C is between 1.1×10^5 and 6.6×10^5 l/mole. Triphenylpyridinium bromide ($TrPyr^{\oplus}Br^{\ominus}$) can be isolated as a colorless salt [3].

In order to investigate the electron-accepting capacity of resonance-stabilized aromatic cations more fully, the behavior of the *N*-2,6-dichlorobenzylquinolinium cation (2,6-DClBQN$^{\oplus}$) was studied. Optical measurements indicate that aromatic amines, even *N,N,N',N'*-tetramethyl-*p*-phenylenediamine, exhibit electron donor-acceptor interaction only at very high concentrations (reversible concentration-dependent red coloration, *e.g.* in $CHCl_3$ and CH_3CN at $c_{salt} = 3 \times 10^{-3}$ mole/l and $c_{amine} = 2 \times 10^{-1}$–1.0 mole/l). Aliphatic amines (n-butylamine, ethanolamine, piperidine, triethylamine), on the other hand, yield completely reversible complexes very readily in $CHCl_3$ [3,4]. These are solvent- and concentration-dependent equilibria which, on addition of HCl, CH_3OH, or H_2O (*i.e.* on raising the dielectric constant) shift

toward the free cations. The ultraviolet spectra of the complexes are largely independent of the nature of the solvent or the amine [6] and are extremely similar to that of 1,2-dihydroquinoline [5].

On addition of increasing amounts of n-butylamine to solutions in $CHCl_3$ of 2,6-DClBQN$^{\oplus}$X$^{\ominus}$ salts, the absorption band at 317 mμ, which is characteristic for the cation, decreases to the same extent as the amount of complex formed. A new absorption band (340 mμ) due to the complex appears with two isosbestic points at 341 and 291 mμ.

The association constants K for a few anions $X^{\ominus}$ are given in Table 1. The increase in the value of K with decreasing size of $X^{\ominus}$ can be attributed to steric causes, since the amine reacts in $CHCl_3$ as an electron donor with the ion pair 2,6-DClBQN$^{\oplus}$X$^{\ominus}$. The infrared spectra of complexes of type *(1)* show broad diffuse bands between 3000 cm^{-1} and 2000 cm^{-1}, which are typical for hydrogen bonds of the NH$^{\oplus}$···X$^{\ominus}$ type [6] and, thus, confirm structure *(1)*.



(1)

Table 1. Association constants of 2,6-DClBQN$^{\oplus}$ X$^{\ominus}$ salts with n-butylamine at 20 °C in $CHCl_3$ in comparison to the thermochemical radii of the anions $X^{\ominus}$.

$X^{\ominus}$	$I^{\ominus}$	$Br^{\ominus}$	$Cl^{\ominus}$	$NO_2^{\ominus}$	$N_3^{\ominus}$
K (l/mole)	7.7	9.0	14.5	28	78
r [A°]	2.20	1.96	1.81	1.55	1.53

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German version: Angew. Chem. *75*, 671 (1963).

[1] *A. G. Evans* et al., Trans. Faraday Soc. *47*, 711 (1951); *50*, 16, 470, 568 (1954); *51*, 481 (1955); *52*, 332 (1956); J. chem. Soc. (London) *1957*, 1021.

[2] *W. Rüttiger*, Ph. D. Thesis, Universität Würzburg, 1957.

[3] *G. Briegleb* and *W. Jung*, unpublished data.

[4] *F. Kröhnke*, Liebigs Ann. Chem. *600*, 21, 176 (1956), suggests the possibility of 2- or 4-addition of piperidine onto cycloimmonium salts.

[5] *W. Jung*, Ph. D. Thesis, Universität Würzburg, 1963.

[6] *G. Briegleb* and *H. Delle*, Z. Elektrochem. *64*, 347 (1960); *R. Mecke* and *W. Kutzelnigg*, ibid. *64*, 1108 (1960).

The Reaction of Camphene with N-Carbonylsulfamyl Chloride

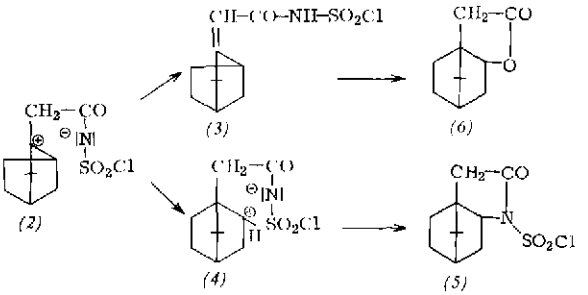
By Dr. habil. R. Graf and Dr. H. Biener

Farbwerke Hoechst AG. formerly Meister Lucius & Brüning, Frankfurt(Main)-Höchst (Germany)

Dedicated to Prof. Dr. Karl Winnacker on the occasion of his 60th birthday

The reaction of camphene with *N*-carbonylsulfamyl chloride *(1)* in ether or liquid SO_2 affords a 70 % yield of a mixture of two isomeric crystalline compounds $C_{11}H_{16}O_3NSCl$, the constitutions of which have been elucidated. The hypothetical primary adduct *(2)* [1] is stabilized either by migration of a proton from the methylene group to the nitrogen atom to give an α,β-unsaturated carboxamide-*N*-sulfonyl chloride *(3)* or by a Wagner-Meerwein rearrangement via *(4)* to a γ-lactam-*N*-sulfonyl chloride *(5)*.

Compound *(3)*, obtained from the crude mixture as the less-soluble component, forms interlinked prisms, m.p. 137 °C (with decomposition). On prolonged boiling with methanol, *(3)* gives an almost quantitative yield of methyl camphene-ω-carboxylate, b.p. 70–72 °C/0.2 mm, an oil of terpene-like odor. The free carboxylic acid, m.p. 126–127 °C ([2] gives 124–125 °C), was obtained by saponification of the ester with methanolic KOH and was converted via the acid chloride into the amide, m.p. 195 °C ([2] gives 192 °C). Hydrolysis of *(3)* by heating with hydrochloric acid affords



$C_{11}H_{16}O_2$ *(6)*, m.p. *ca.* 200 °C, a readily sublimable, camphor-like, isotropic substance. The reactions and nuclear magnetic resonance spectrum of *(6)* characterize it as a γ-lactone, resulting from a Wagner-Meerwein rearrangement, via a β-hydroxy carboxylic acid.

Compound *(5)*, colorless needles m.p. 126 °C, can be recrystallized unchanged from methanol, even after prolonged boiling, and is thus readily separated from *(3)*. A diamino derivative $C_{23}H_{41}O_3N_3S$, colorless needles, m.p. 224 °C from methanol, is obtained with cyclohexylamine. Redoxhydrolysis [1] of *(5)* in methanol/water results in an almost quantitative yield of a γ-lactam $C_{11}H_{17}ON$ *(7)*, platelets, m.p. 190 °C (isotropic) from hot water; the crystals contain water of crystallization and effloresce readily. It is hydrolysed only on prolonged boiling with conc. hydrochloric acid to yield the hydrochloride of an amino acid $C_{11}H_{19}O_2N$ (m.p. 210 to 220 °C, with decomposition), whose ethyl ester reforms the lactam *(7)* when heated with sodium ethoxide. The *N*-carbamyl-lactam (fine needles from methanol, m.p. 185 °C, anisotropic) obtained by hydrolysis of the reaction product obtained from interaction of *(7)* and *(1)* is not rearranged to a dihydrouracil derivative on heating with conc. hydrochloric acid, and an alternative β-lactam structure is thus excluded. In addition, the nuclear magnetic resonance spectra of *(5)* and *(7)* clearly favor the five-membered ring structure.

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[1] *R. Graf*, Liebigs Ann. Chem. *661*, 111 (1962).

[2] *M. G. Langlois*, Ann. Chimie (9) *12*, 193 (1919).

Organotin Phosphides

By Dr. H. Schumann, Dipl.-Chem. H. Köpf, and Prof. Dr. Max Schmidt

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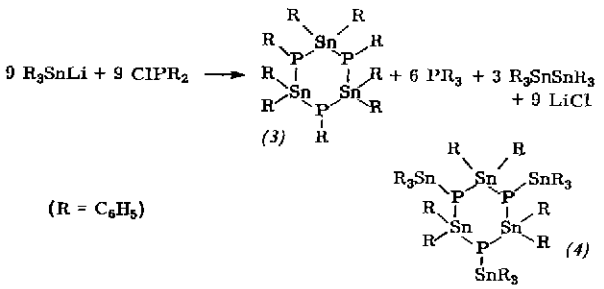
A publication on organogermanium compounds [1] prompts us to report briefly on the synthesis of the corresponding organotin compounds, for only a single representative of these has been mentioned to date [2]. When tetraphenyltin is treated with elementary phosphorus, various organotin phosphides are formed, depending on the temperature and concentration ratio of the starting materials. These can also be prepared in three other ways: 1. From diorganyl-lithium phosphide and an organotin halide, 2. from diorganylphosphines and an organotin halide in the presence of a tertiary amine, and 3. from a lithium triorganyltin and an organochlorophosphine. Methods 1 and 2 yield, for instance, $(C_6H_5)_2P-Sn(C_6H_5)_3$ *(1)*, m.p. 126 °C, and $(C_6H_5)_2P-Sn(C_4H_9)_3$ *(2)*, m.p. 60 °C, while method 3 leads, for example, to *(3)*, m.p. 64 °C.

If $RPCl_2$ is used, one obtains *(4)*, m.p. 99 °C.



$(R = C_6H_5)$

Compounds *(1)*, *(3)*, and *(4)* can also be prepared directly from SnR_4 and phosphorus. They are rapidly oxidized in air to organotin phosphates [*(1)* and *(2)* more readily than *(3)* and *(4)*], and are cleaved into characteristic fragments by alcoholic NaOH. The phosphorus atoms can be methylated readily with CH_3I.

Received, June 18th, 1963 [Z 525/359 IE]
German version: Angew. Chem. *75*, 672 (1963).

[1] *F. Glockling* and *K. A. Hooton*, Proc. chem. Soc. (London) *1963*, 146.

[2] *W. Kuchen* and *H. Buchwald*, Chem. Ber. *92*, 227 (1959).

The Mobility of the Hydride Hydrogen Atom in Trialkyltin, -germanium, and -silicon Hydrides

By Priv. Doz. Dr. W. P. Neumann
and Dipl.-Chem. R. Sommer

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Organotin hydrides readily add onto olefins, alkynes, azomethines, and carbonyl compounds [1] by both radical [2,3] and ionic [3,4] mechanisms. This induced us to investigate the mobility of the hydride hydrogen atom in organotin hydride molecules. When equimolar quantities of tri-isobutyltin hydride *(1)* and triethyltin deuteride *(2)* were mixed at 40 °C without a catalyst (*e.g.* traces of aluminum alkyls), complete equilibration according to (a) had occurred after only 25 minutes (Table 1):

(a) $R'_3SnH + R_3SnD \rightleftharpoons R'_3SnD + R_3SnH$
(1) *(2)* *(3)* *(4)*

Table 1. H-D exchange according to reaction (a) between equimolar quantities of $(i\text{-}C_4H_9)_3SnH$ and $(C_2H_5)_3SnD$. Each value has been obtained by a separate experiment.

Time [min]	1.8	5.4	10.9	22.7
$(C_2H_5)_3SnH$ *(4)* [mole-%]	4.2	11	19	24

The preheated substances were pipetted under argon into a distillation apparatus (previously warmed to 40 °C), and then stirred. After a given time (see Table 1), the pressure was suddenly reduced to 12 mm, whereupon some *(2)* and triethyltin hydride *(4)* passed over within a few seconds. The latter was estimated by infrared spectroscopy at 1805–1815 cm^{-1}.

Trialykltin deuterides prepared analogously to the production of the hydrides [5] from trialkyltin chlorides and diethylaluminum deuteride [6] were:

$(C_2H_5)_3SnD$ *(2)*: b.p. 35–37 °C/11 mm, $n_D^{20} = 1.4702$, $\nu_{SnD} = 1304\ cm^{-1}$

$(i\text{-}C_4H_9)_3SnD$ *(3)*: b.p. 104–106 °C/11 mm, $n_D^{20} = 1.4697$, $\nu_{SnD} = 1302\ cm^{-1}$

$(C_6H_5)_3SnD$ [7]: b.p. 152–156 °C/0.002 mm (Crystalline at 20 °C), $n_D^{28} = 1.6318$, $\nu_{SnD} = 1323\ cm^{-1}$

H-D exchange between *(2)* and an equimolar quantity of diisobutylaluminum hydride as in (b) leads to equimolar quantities of *(2)* and *(4)* after less than 3 minutes at 50 °C.

We might assume an analogous transition state also for reaction (a). Its stationary concentration must however be low; molecular-weight determinations of trialkyltin hydrides gave the monomeric formula weight [1].

(b) $R_3SnD + \frac{1}{3}(R'_2AlH)_3 \rightleftharpoons \left[R_3Sn(D)(H)AlR'_2\right] \rightleftharpoons R_3SnH + \frac{1}{3}(R'_2AlD)_3$
(2) *(4)*

An equilibrium similar to (b) did not occur, even at 60 °C, when triethylsilicon hydride or triethylgermanium hydride was stirred with an equimolar quantity of diethylaluminum deuteride at 60 °C.

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German version: Angew. Chem. *75*, 788 (1963).

[1] Review: *W. P. Neumann*, Angew. Chem. *75*, 225 (1963); Angew. Chem. internat. Edit. *2*, 165 (1963).

[2] *W. P. Neumann*, *H. Niermann*, and *R. Sommer*, Angew. Chem. *73*, 768 (1961); Liebigs Ann. Chem. *659*, 27 (1962); *R. Calas*, *J. Valade*, and *J. C. Pommier*, C. R. hebd. Séances Acad. Sci. *225*, 1450 (1962).

[3] *W. P. Neumann* and *E. Heymann*, Angew. Chem. *75*, 166 (1963); Angew. Chem. internat. Edit. *2*, 100 (1963).

[4] *J. G. Noltes* and *G. J. M. van der Kerk* [Chimia *16*, 122 (1962); additional references given therein] assume an ionic mechanism for the uncatalysed addition onto olefins.

[5] *W. P. Neumann*, Angew. Chem. *73*, 542 (1961); *W. P. Neumann* and *H. Niermann*, Liebigs Ann. Chem. *653*, 164 (1962).

[6] *G. Wilke* and *H. Müller*, Liebigs Ann. Chem. *618*, 267 (1958).

[7] *H. G. Kuivila*, *L. W. Menapace*, and *C. R. Warner* [J. Amer. chem. Soc. *84*, 3584 (1962)] mention this substance but without giving details of its preparation or properties.

Organometal-catalysed Additions of Organotin Hydrides onto α-Olefins

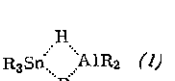
By Priv.-Doz. Dr. W. P. Neumann, Dr. H. Niermann [1], and cand. chem. B. Schneider

Chemisches Institut der Universität Giessen (Germany)

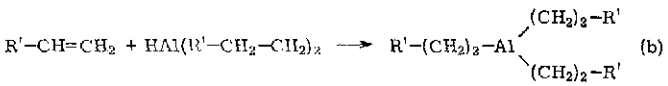
We have found that on mixing alkyltin hydrides with aluminum trialkyls, an alkyl residue is exchanged for hydrogen as in (a):

$$R_3SnH + AlR_3 \rightarrow R_4Sn + HAlR_2 \qquad (a)$$

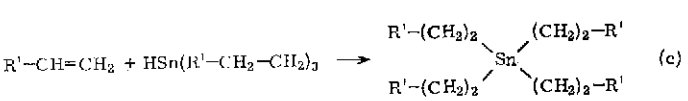
For example, with equimolar proportions of the ethyl compounds (in an inert atmosphere), exchange occurs within 20 min at 80 °C. The reverse reaction does not occur. Ethyl, n-butyl, and n-octyl groups react at about the same rate; isobutyl groups react somewhat slower. Ethers and tertiary amines inhibit the reaction. The electron-deficient state of the aluminum is thus important and *(1)* is a probable transition state.



If an α-olefin is added, AlR_3 is regenerated [2] according to (b).



The net reaction is addition of the organotin hydride onto the α-olefin with AlR_3 merely acting as catalyst:



$HAlR_2$, $LiAlR_4$, ether-free AlH_3 [3], and $LiAlH_4$ may be used instead of AlR_3. In these compounds, R should correspond to the olefin. Otherwise the wrong group must be "displaced" first [4].

Reactions of type (c) are known [5] and can be catalysed by radical-formers [6]. The advantage of this new "intermediate-catalysis" is evident in the particularly smooth reaction of aliphatic organotin hydrides with unsubstituted α-olefins and dienes. For example, propylene reacts according to (c) at 70–80 °C and normal pressure. Table 1 gives further examples. The reactions are usually complete within 3 hours. The first hydrogen atom of an alkyltin trihydride reacts faster than that of a dialkyltin dihydride, which in turn reacts faster than that of a trialkyltin hydride.

Table 1. Products from α-olefins and alkyltin hydrides [a].

Product	Obtained from	b.p. [°C/mm]	Yield [%]
$(C_2H_5)_3SnC_8H_{17}$	1-octene + $(C_2H_5)_3SnH$	142/9	90
$(C_2H_5)_3Sn(CH_2)_2$—⟨ ⟩	H_2C=CH—⟨ ⟩ + $(C_2H_5)_3SnH$	82/0.15	80
$(C_2H_5)_3Sn(CH_2)_3Sn(C_2H_5)_3$	$(C_2H_5)_3SnCH_2CH$=CH_2 + $(C_2H_5)_3SnH$	110/0.2	68
$(C_4H_9)_2Sn[(CH_2)_6$—CH=$CH_2]_2$	1,7-octadiene [b] + $(n\text{-}C_4H_9)_2SnH_2$	135/10^{-3}	73
iso-$C_4H_9Sn(C_8H_{17})_3$	1-octene + iso-$C_4H_9SnH_3$	180/10^{-2}	59

[a] Obtained at 60–85 °C with exclusion of air generally using 1–5 mole-% catalyst.
[b] 8-fold excess; the dibutyltin dihydride was added slowly dropwise.

With poly-unsaturated compounds, poly-addition may be effected. This provides a novel route to organic polymers with tin in the main chain [5,6] as in (d):

$$n\,H_2C{=}CH{-}(CH_2)_4{-}CH{=}CH_2 + (n\text{-}C_4H_9)_2SnH_2$$

$$\text{(d)} \qquad \xrightarrow{AlR_3} \quad \left[-(CH_2)_8{-}(C_4H_9)_2Sn-\right]_n$$

With trifunctional reactants, such as iso-$C_4H_9SnH_3$, partially or fully cross-linked polymers are obtained.

Received, July 1st, 1963 [Z 536/362 IE]
German version: Angew. Chem. 75, 790 (1963).

[1] *H. Niermann*, Ph.D.Thesis, Universität Giessen, 1961.

[2] *K. Ziegler, H.-G. Gellert, H. Martin, K. Nagel*, and *J. Schneider*, Liebigs Ann. Chem. *589*, 91 (1954); further literature references are given in this paper.

[3] *E. Wiberg, H. Graf, M. Schmidt*, and *R. Uson*, Z. Naturforsch. *7b*, 578 (1952); *G. Chizinsky, G. G. Evans, T. R. P. Gibb jr.*, and *M. J. Rice jr.*, J. Amer. chem. Soc. *77*, 3164 (1955); our samples made according to the latter paper contained about 40% $H_3Al{\cdot}OR_2$.

[4] *K. Ziegler, H. Martin*, and *F. Krupp*, Liebigs Ann. Chem. *629*, 14 (1960); further literature references are given in this paper.

[5] *G. J. M. van der Kerk, J. G. A. Luijten*, and *J. G. Noltes*, Angew. Chem. *70*, 298 (1958); further literature references are given in this paper; see also [6].

[6] *W. P. Neumann, H. Niermann*, and *R. Sommer*, Angew. Chem. *73*, 768 (1961); Liebigs Ann. Chem. *659*, 27 (1962); *W. P. Neumann*, Angew. Chem. *75*, 225 (1963); Angew. Chem. internat. Edit. *2*, 165 (1963).

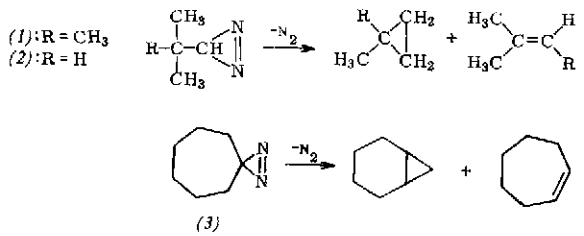
Diazirines as Carbene Precursors

By Doz. Dr. Ernst Schmitz, Dipl.-Chem. D. Habisch, and cand. chem. A. Stark

Institut für Organische Chemie der Deutschen Akademie der Wissenschaften, Berlin-Adlershof (Germany)

The most certain indication of the occurrence of carbenes is given by intramolecular formation of cyclopropane by insertion into a γ-C–H-bond [1,2]. We have shown that thermal decomposition of diazirines gives rise to carbenes and nitrogen. We have prepared the diazirines *(1)*, *(2)*, and *(3)*. These decompose when added dropwise to boiling nitrobenzene to give 92–95% yields of volatile compounds which were separated by gas chromatography and identified by comparison with authentic materials.

Compound *(1)*, b.p. 61–62 °C, afforded 80% 1,1-dimethylcyclopropane and 20% trimethylethylene; *(2)*, b.p. 38–42 °C, gave the corresponding methylcyclopropane (51%) and isobutylene (49%); hexamethylenediazirine *(3)*, b.p. 41–41.5 °C/12 mm, gave 18% norcarane and 82% cycloheptene.



(3)

The products and the yields of cyclopropanes are similar to those obtained from carbenes generated by alkaline decomposition of tosyl hydrazones [1,3] or by the action of sodium on primary alkyl chlorides [2].

In the carbene reactions of diazirines, a definite compound is treated under neutral conditions. In contrast to the previous modes of formation of carbenes, the solvent exerts no influence on the distribution of the products: thermal decomposition of *(1)* and *(2)* gave identical yields of the appropriate cyclopropane and olefin in both hydroxylic and non-hydroxylic solvents.

Received, June 24th, 1963 [Z 529/354 IE]
German version: Angew. Chem. 75, 723 (1963)

[1] *L. Friedman* and *H. Shechter*, J. Amer. chem. Soc. *81*, 5512 (1959).

[2] *W. Kirmse* and *W. v. E. Doering*, Tetrahedron *11*, 266 (1960).

[3] *L. Friedman* and *H. Shechter*, J. Amer. chem. Soc. *83*, 3159 (1961).

Spectrophotometric Detection of Charge Transfer Complexes with Sulfur Dioxide as Acceptor and Iodide or Iodine as Donor [1]

By Prof. Dr. J. Jander and Dipl.-Chem. G. Türk

Chemisches Laboratorium der Universität Freiburg/Breisgau and Anorganisch-Chemisches Laboratorium der Technischen Hochschule München (Germany)

We have carried out spectrophotometric studies of the influence of the cation, the temperature, the pH (in aqueous solution), and the solvent on the spectra of solutions of the well-known [1a] yellow adducts of SO_2 and alkali metal iodides. At 20 °C, the absorption spectrum of an aqueous KI/SO_2 solution (c_{KI} = 0.1 M; $c_{SO_2} = 8.4\times10^{-3}$ M) shows a wide charge-transfer band with a maximum at 341 mμ. The half band-width is 6800 cm^{-1}. The absorption maximum of an aqueous NaI/SO_2 solution shows only a slight shift: λ_{max} = 337 mμ. The influence of the cation on the spectrum is therefore practically negligible [2]. The maximum of the band of an aqueous KI/SO_2 solution (c_{KI} = 0.1 M; $c_{SO_2} = 5\times10^{-3}$ M) is shifted from 341 mμ at +31.8 °C to 335 mμ at + 1 °C, *i.e.* it drifts towards shorter wavelengths with decreasing temperature. Any lowering of the pH leads to a marked increase in extinction at 341 mμ, owing to the consequent increase in the concentration of SO_2. At +22.6 °C, the absorption maximum of a KI/SO_2 solution in methanol (c_{KI} = 0.1 M; $c_{SO_2} = 1.8\times10^{-3}$ M) lies at 355 mμ; at −31.7 °C, it lies at 347 mμ. The bands are therefore shifted towards the red in methanol (compared with water as solvent).

Using an optical method according to *Briegleb* [3], we were able to prove the existence of a 1:1-complex ISO_2^- in aqueous solution. The stability constant of this weak complex can be estimated to be $K_c^{20°} \approx 1.0$ l/mole. From solubility data [4] we calculated $K_c^{25°} \approx 0.8$ l/mole.

The results show [5] that the yellow adducts are charge transfer complexes of the *Mulliken* type [6], in which the iodide ions act as donors and the SO_2^- molecules as acceptors. Infrared spectroscopic measurements in acetonitrile led to the same result [2]. It was possible to calculate the complete term diagram of the complex [5,7]: $W_N = \Delta H = -1.68$, $W_0 = -0.12$, $W_1 = 77.68$, $W_E = 82.16$ kcal/mole. Although we failed to obtain any indication of an addition compound in the course of tensimetric analysis of a solution of iodine in liquid SO_2 at −61.5 °C [8], low-temperature spectra of this solution ($\gamma_{I_2} = 7.7 \times 10^{-5}$) did show a definite shift of the iodine bands towards the blue; this shift increases with decreasing temperature. The maximum value for the iodine band is 493.5 mμ at −14.7 °C, 490 mμ at −41.8 °C, and 482.5 mμ at −73.5 °C. The bathochromic shift of the iodine band is taken as definite evidence for the formation of a charge transfer complex according to the equation:

$$x\ I_2 + y\ SO_2 \rightleftharpoons (I_2)_x \cdot (SO_2)_y.$$

The stoichiometric relationships of the complex are still unknown; its stability is low. Its enthalpy of formation at −15 °C is estimated [5] at $\Delta H \approx -2$ kcal/mole and therefore corresponds to the stability of iodine/aromatic complexes. In this complex, the iodine molecule acts as donor, the SO_2 molecule as acceptor. There are some other instances of this unusual donor function of the iodine molecule, *viz.* the autocomplex of iodine I_4 [9] and the complex cation I_3^+ [10].

Received, July 16th, 1963 [Z 544/370 IE]
German version: Angew. Chem. 75, 792 (1963).

[1] Part III of the series on Sulfur-Iodine Compounds; Part II: *J. Jander* and *G. Türk*, Chem. Ber. *95*, 2314 (1962).

[1a] Gmelins Handbuch der anorganischen Chemie. 8th Edit., Verlag Chemie, Berlin 1933, Vol. Iodine, p. 401.

[2] See also *E. R. Lippincott* and *F. Eugene*, Spectrochim. Acta (London) *17*, 123 (1961).

[3] *G. Briegleb:* Elektronen-Donator-Acceptor-Komplexe. Moleküle und Koordinationsverbindungen in Einzeldarstellungen, Springer-Verlag, Berlin 1961, p. 199ff.

[4] *C. J. J. Fox*, Z. physik. Chem. *41*, 458 (1902).

[5] *G. Türk*, Ph. D. Thesis, Universität Freiburg/Breisgau, 1963.

[6] *R. S. Mulliken*, J. physic. Chem. *56*, 801 (1952).

[7] For an explanation of the individual energy values, see [3,] p. 3.

[8] See also *G. Jander* and *H. Mesech*, Z. physik. Chem. *183A*, 121 (1939).

[9] *G. Kortüm* and *H. Koffer*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *67*, 67 (1963).

[10] *J. Arotsky, H. C. Mischra*, and *M. C. R. Symons*, J. chem. Soc. (London) *1962*, 2582.

Detergent Action of Hydroxylated Fatty Esters of Sucrose

By Dr. H. Simonis and Dr. R. M. Ismail

Forschungslaboratorium der Firma H. J. Zimmer, Frankfurt/Main (Germany)

Fatty esters of sucrose containing one or more hydroxyl groups in the fatty acid residue are characterized not only by outstanding detergent action but are also completely degraded by bacteria [1]. The monohydroxy-, dihydroxy-, and trihydroxystearic esters of sucrose, whose even-numbered fatty acid residues contain 14–22 carbon atoms, were prepared by hydroxylation of fatty esters and catalysed transesterification with sucrose [2,3] in a polar solvent. The resulting mixtures contained about 75 % mono- and about 25 % diester. The compounds given in Table 1, for example, were prepared.

Table 1. Properties of hydroxylated fatty esters of sucrose.

Fatty acid	M.p. [°C]	Surface tension [a] [dynes/cm]	Wetting [b] power [g/l]
12-Hydroxystearic	58.5-61.5	33.3	0.40
9,10-Dihydroxystearic	49.0-51.8	31.4	0.40
9,10,12-Trihydroxystearic	55.0-58.5	33.5	1.0
Ricinoleic	56.0-60.5	36.5	0.50

[a] Measured at 60 °C in 0.1 percent aqueous solutions.
[b] After 100 seconds.

Received, July 5th, 1963 [Z 539/363 IE]
German version: Angew. Chem. 75, 791 (1963).

[1] Studies under the direction of Prof. *Kölbel*, Berlin, and Prof. *Schlegel*, Göttingen, for which we again express thanks.

[2] *L. Osipow, F. dee Snell, D. Marra*, and *W. C. York*, Ind. Engng. Chem. *48*, 1459 (1956).

[3] *G. R. Ames*, Chem. Reviews *60*, 541 (1960).

CONFERENCE REPORTS

Meeting of Northwest-German Chemistry Lecturers

Braunschweig (Germany), May 18th and 19th, 1963

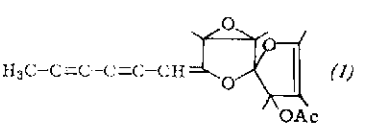
From the proceedings:

A Naturally Occurring Epoxide with Diyne and Enol Ether Functions

C. Arndt, Berlin (Germany)

In addition to several other spiroketals containing enol ether and poly-yne functions which were isolated in previous investigations on material from *Chrysanthemum leucanthemum* L., a minute amount of a compound was obtained whose structure was not determined.

The molecular formula was found to be $C_{15}H_{12}O_5$. Besides the enol ether bands, only an acetyl residue can be recognized as a functional group from its infrared spectrum. Since this substance has one oxygen atom more than previous compounds in this series, this oxygen must be in an ether bond. On ozonisation, as expected, 3,5-heptadiynoic acid was produced. Very mild saponification yielded an alcohol. Reaction with sodium methoxide gave a diol with an ether grouping. Since epoxides in the allylic position are split by sodium methoxide, structure *(1)* would be a possibility for the epoxide.



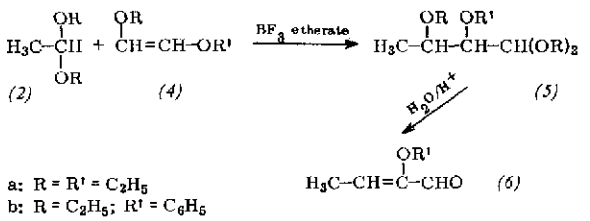
(1)

Nuclear magnetic resonance spectra of the natural material and of its reaction products are in complete agreement with this formulation.

Addition Reactions of 1,2-Dialkoxyethylene

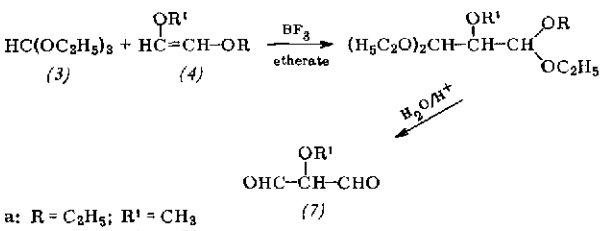
H. Baganz, Berlin (Germany)

Acetaldehyde diethylacetal *(2)* and triethyl orthoformate *(3)* can be added, under the catalytic influence of boron trifluoride etherate, onto symmetrically substituted ethylene derivatives of type *(4)*. The addition yields the corresponding α,β-dialkoxybutyraldehyde dialkylacetals *(5)* which can be hydrolysed to give the hitherto unknown α-alkoxycrotonaldehydes *(6)*.



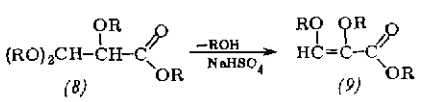
a: $R = R' = C_2H_5$
b: $R = C_2H_5$; $R' = C_6H_5$

The addition of *(3)* allowed a simple synthesis of triosereductone-2-ethers *(7)*.



a: $R = C_2H_5$; $R' = CH_3$
b: $R = C_2H_5$; $R' = C_2H_5$
c: $R = C_2H_5$; $R' = C_6H_5$

Addition of *(3)* onto 1-chloro-1,2-diethoxyethylene gave α,β,β-triethoxypropionate *(8)* which was converted by elimination of alcohol into α,β-diethoxyacrylate *(9)*

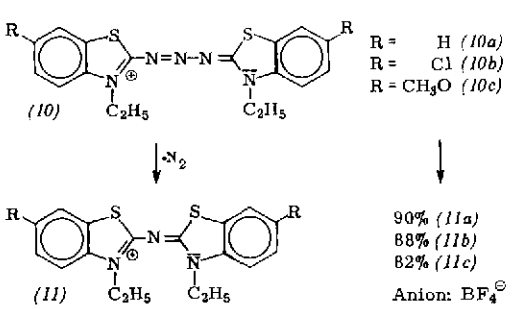


Addition of chlorine onto *(9)* yielded 1,2-dichloro-1,2-diethoxypropionate, and this was converted by alcoholysis into α,α,β,β-tetraethoxypropionate. The infrared spectra of these two esters show a carbonyl absorption band at 1770 cm^{-1}.

The Conversion of Triazatrimethinecyanine Dyes into Azamonomethinecyanines

H. Balli, Karlsruhe (Germany)

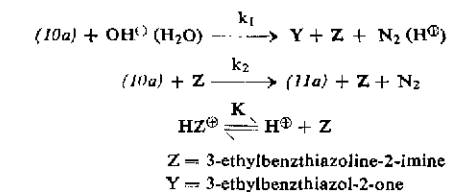
Benzthiazolyltriazatrimethinecyanines *(10)* are, in the main, stable in anhydrous inert solvents (*e.g. o*-dichlorobenzene or benzonitrile) even at high temperatures, but in aqueous media they decompose into azomonomethinecyanines *(11)* with loss of nitrogen.



R = H *(10a)*
R = Cl *(10b)*
R = CH_3O *(10c)*

90% *(11a)*
88% *(11b)*
82% *(11c)*
Anion: $BF_4^{\ominus}$

The decomposition of compound *(10a)* with $ClO_4^{\ominus}$ as anion at 80 °C in water/dimethyl sulfoxide buffered by the system ethyldiisopropylamine/ethyldiisopropylammonium perchlorate was followed spectrophotometrically. The observed reaction kinetics can be assigned to a competitive system:



Z = 3-ethylbenzthiazoline-2-imine
Y = 3-ethylbenzthiazol-2-one

The apparent reaction rate constants

$$a = k_1\,[OH^{\ominus}] + k_1'\,[H_2O] \quad \text{and} \quad b = k_2 \cdot \frac{K}{K + [H^{\oplus}]}$$

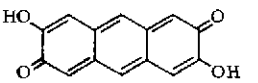
were found from the integrated differential equation to have the values

$$a = (6.3 \pm 0.2) \times 10^{-3}\ [min^{-1}],\ b = 8.1 \pm 0.4\ [l \cdot mole^{-1}\ min^{-1}]$$

New Hydroxyanthraquinones

P. Boldt, Göttingen (Germany)

Dehydrogenation of 2,3,6,7-tetrahydroxyanthracene *(12)* with 2,3-dicyano-5,6-dichlorobenzoquinone or lead dioxide in dioxan leads to a pale yellow, unstable compound, which judging by its reactions and from its method of preparation must be the 3,7-dihydroxy derivative *(13)* of the previously unknown compound 2,6-anthraquinone.

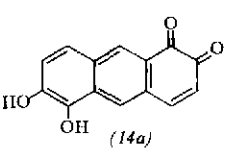


(13)

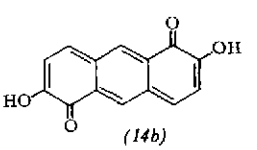
Formulation as 6,7-dihydroxy-2,3-anthraquinone is ruled out on grounds of analogy.

Compound *(12)* was previously undescribed and was prepared by reduction of 2,3,6,7-tetrahydroxy-9,10-anthraquinone with sodium borohydride in 1 N sodium carbonate solution.

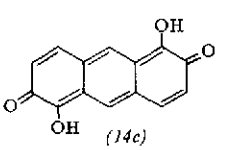
Reaction of 2 moles of tetrabromo-*o*-benzoquinone with 1,2,5,6-tetrahydroxy-9,10-dihydroanthracene *(15)* afforded a stable, dark blue dihydroxyanthraquinone *(14)*; three tautomeric quinonoid structures, *viz. (14a)–(14c)*, are possible for this compound.



(14a)

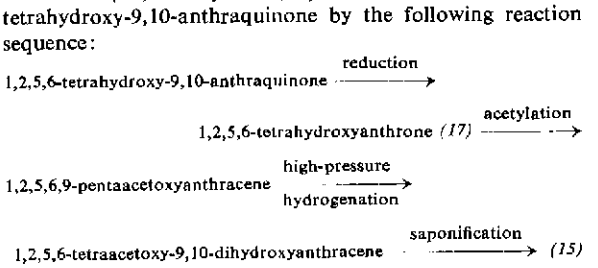


(14b)

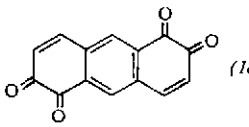


(14c)

Some findings (pK-value, infrared spectrum, preparation of a methyl ether with hydrochloric acid in methanol) favor the forms *(14b)* and *(14c)*, while others (preparation of a diacetate, redox potential) favor *(14a)*. A decision between these forms is expected from a closer study of the methyl ether. Reductive acetylation of *(14)* gave 1,2,5,6-tetraacetoxyanthracene *(16)*. Compound *(15)* was prepared from 1,2,5,6-tetrahydroxy-9,10-anthraquinone by the following reaction sequence:



Use of 3 moles of quinone for the dehydrogenation of *(15)* led to stable 1,2,5,6-anthradiquinone *(18)*, which is the first anthradiquinone without substituents in the *meso*-positions.



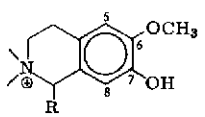
(18)

Reductive acetylation of *(18)* led to *(16)*, and condensation with *o*-phenylenediamine gave a compound containing two quinoxaline rings. Analogous dehydrogenation of the anthrone *(17)* led to two stable anthraquinones, which differ from *(14)* and *(18)* by possession of a hydroxyl group in the 9-position.

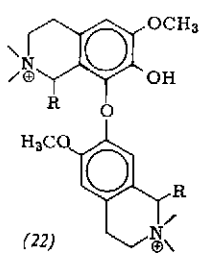
New Biogenetic-type Alkaloid Syntheses

B. Franck, Göttingen (Germany)

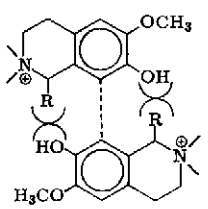
Hydroxylated 1-benzyl- and 1-alkyl-tetrahydroisoquinolines can be made to undergo oxidative condensation in a manner resembling that occurring in alkaloid biosynthesis if their nitrogen atom is protected by quaternization. Simple syntheses of various aporphines [1], of dibenzyltetrahydroisoquinoline alkaloids of the berbamine type [2], and of the cactus alkaloid pilocereine have been achieved in this way. Of the many possible modes of condensation of the intermediary mesomeric radicals, only those forming naturally occurring alkaloids proceeded in good yield and with few by-products. Thus, quaternary derivatives of coclaurine *(19)*, *(20)* and lophocerine *(21)* gave dimeric condensation products with a diphenyl-ether linkage *(22)* on oxidation with one equivalent of ferric chloride or potassium ferricyanide, although C–C condensation to give *(23)* should be preferred [3].



(19) R = *p*–HO–C_6H_4–CH_2–
(20) R = *p*–H_3CO–C_6H_4–CH_2–
(21) R = $(CH_3)_2CH$–CH_2–



(22)



(23)

This unusual formation of diphenyl ethers from *(19)*–*(21)* is due to the fact that the mesomer with the radical at C-8 produced on oxidation of the hydroxyl at C-7 is sterically hindered and can condense with a second isoquinoline residue only if the latter is kept at a distance by an oxygen atom between the residues. This explains why all the 62 bisbenzyltetrahydro-isoquinoline alkaloids previously isolated have the two halves of the molecule joined by an ether bridge.

[1] *B. Franck* and *G. Schlingloff*, Liebigs Ann. Chem. *659*, 123 (1962).

[2] *B. Franck* and *G. Blaschke*, Liebigs Ann. Chem., in the press.

[3] *D. H. R. Barton* and *T. Cohen* in: Festschrift Arthur Stoll. Birkhäuser, Basel (Switzerland) 1957, p. 122.

Low Coordination Numbers in Thermally Decomposed Hydroxides

F. Freund, Göttingen (Germany)

Hydroxides can be decomposed thermally at relatively low temperatures. Fine-grained substances, amorphous to X-rays, often result, whose general chemical and physical properties are determined by their large specific surface area. By investigating the irreversible transformations often observed with these X-ray-amorphous substances, it was established that the substances in the powder diagram appear to be amorphous but that the individual particles are paracrystalline. In some cases it was observed that the structural elements of the starting material were retained to a large extent in the dehydrated product. This is only possible, if the structure-forming coordination polyhedron remains almost unchanged. While the coordination polyhedron of the starting substance has for example 4 hydroxyl groups and 2 oxygens as ligands of the central cation, after dehydration there are only 4 oxygen ligands. The lattice sites which became vacant remain empty. Such an arrangement is unstable.

In kaolinite, where Al^{3+} is surrounded by 4 hydroxyl groups and 2 oxygen atoms, after dehydration the coordination number is 4. A significant drop in coordination number has also been detected in dehydrated aluminum hydroxide where the instability becomes especially marked. At higher temperatures, the Al^{3+} partly changes into the more stable 6-coordination, thus forming new crystalline phases.

The Solubility of Silicates

H. Funk, Berlin (Germany)

It was found, that monosilicates are converted by HCl into monosilicic acid, which readily dissolves in solvents forming hydrogen bonds.

$$Ca_2SiO_4 + 4\,HCl = Si(OH)_4 + 2\,CaCl_2$$

Disilicates are also very soluble; trimetasilicates, by comparison, are only sparingly soluble, while polysilicates are insoluble. The nature of the cation also influences the solubility; the particle size has little effect. The hydrated calcium silicates formed by hydration of Ca_3SiO_5 and Ca_2SiO_4 cause cement hardening, are monomeric and polymerize on heating. $Si(OH)_4$ dissolved in non-aqueous solvents may form equilibria, in which either highly soluble silicic acids of low molecular weights predominate, or intermediate condensation stages consisting of clear, viscous solutions or transparent gels of high molecular weights are formed. The condensation of $Si(OH)_4$ is influenced by the concentration, the temperature, the hydrogen ion concentration, and the type of solvent.

Bismuth Oxides

G. Gattow, Göttingen (Germany)

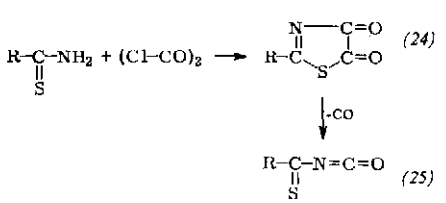
The polymorphism of bismuth(III) oxide was investigated by means of differential thermal analysis, temperature *vs.* time diagrams, X-ray photographs, and crystal structure analysis. Monoclinic α-Bi_2O_3 is transformed to the high-temperature modification (δ-Bi_2O_3) at 720 °C and melts at 824 °C. δ-Bi_2O_3 crystallizes in the cubic system ($a = 5.665 \pm 0.005$ Å at 750 °C) and has the CaF_2 structure with an oxygen-deficient lattice ($R_{hkl} = 0.019$). On cooling the melt, the transformation δ-$Bi_2O_3 \rightarrow \beta$-$Bi_2O_3 \rightarrow \alpha$-$Bi_2O_3$ occurs. The β-modification can be prepared as a metastable phase at room temperature by very rapid chilling. It crystallizes in the tetragonal system ($a = 10.95 \pm 0.05$, $c = 5.63 \pm 0.01$ Å) space group $P\bar{4}b2$-D_{2d}^7. β-Bi_2O_3 is a two-dimensional superstructure of δ-Bi_2O_3 in which each bismuth atom is surrounded by 6 oxygen atoms at distances of 2.40 Å in the form of a severely distorted octahedron ($R_{hkl} = 0.046$).

On burning elemental bismuth or a mixture of Bi_2O_3 + C in a carbon boat (> 800 °C; strong O_2-stream), an oxygen-enriched Bi(III) oxide results, which gives an X-ray diagram that is practically the same as that of β-Bi_2O_3. From its crystal structure it can be deduced that the β-modification can continuously absorb up to half an atom of oxygen per mole of Bi_2O_3 without alteration of the lattice symmetry (a = 10.96 ± 0.02, c = 5.64 ± 0.01 Å; R_{hkl} = 0.052). The phases of the β-modification vary from $BiO_{1.50}$ to $BiO_{1.75}$. The $BiO_{1.75}$ can be transformed into α- or β-Bi_2O_3 or into the cubic γ-phase ($BiO_{>1.50}$).

Thioacyl Isocyanates

J. Goerdeler and *H. Schenk*, Bonn (Germany)

Aromatic thioamides can be converted into thiazolinediones *(24)* by means of oxalyl chloride [4].



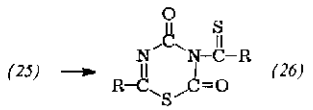
(24)

(25)

The latter undergo thermolysis, with elimination of carbon monoxide to form highly reactive, colored thioacyl isocyanates *(25)*.

The addition of nucleophiles HX – so far chiefly amines and amides – yields a series of previously mostly unknown thioacyl derivatives, R–C(S)–NH–C(O)–X, which can in turn be cyclized to heterocyclic products (triazoles, thiadiazoles, triazines). Displacements, *e.g.* of diphenylamine by nitraniline, were observed.

Compounds of formula *(25)* undergo 1,4-cycloaddition with suitable polar multiple-bond systems. Their spontaneous dimerization in solution is an example of this type:



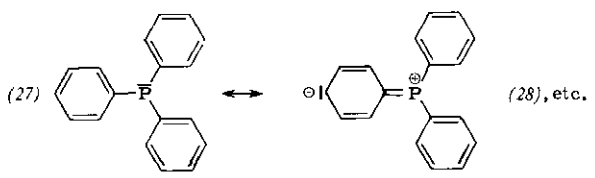
(25) *(26)*

The structure of the deep-violet crystalline compound *(26)* was proved, *inter alia* by a thermal degradation reaction. Compound *(26)* represents a new type of dimeric isocyanate.

The Influence of Substituents on the Charge Distribution in Some Triarylphosphines and Their Derivatives

H. Goetz, Berlin (Germany)

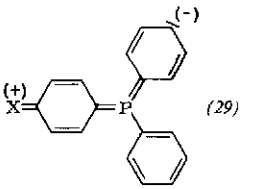
Investigations of the dipole moments of some *p*-X-phenyldiphenylphosphines, where X = H, Cl, Br, OCH_3, or $N(CH_3)_2$, show that the mesomerism which has hitherto been assumed to occur in triphenylphosphine, *viz.*:



(27) *(28)*, etc.

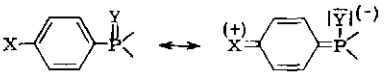
does not fully describe the true mesomeric state of the phosphines investigated. In these compounds, a third limiting structure must be assumed, *viz.*

The participation of *(28)* and *(29)* is small, although the formal participation of *(29)* rises perceptibly with increasing ability of X to act as an electron-donor, *i.e.* in the series Cl ≤ Br < OCH_3 < $N(CH_3)_2$. Furthermore, examination of



(29)

the ultraviolet spectra shows that *(28)* and *(29)* are probably involved in the mesomerism of the optically excited state. However, as the character of X as an electron donor increases, here the formal participation of *(28)* decreases in favor of *(29)*. The ultraviolet spectra of phosphine oxides and sulfides suggest that the mesomerism



(30), Y = O, S

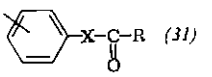
occurs in the optically excited state. Here, too, the participation of *(30)* decreases with increasing electron-donor properties of X.

Alkaline Hydrolysis of Phenyl Hydrocinnamates, Phenyl Thiohydrocinnamates, and Phenyl Selenohydrocinnamates

J. Gosselck, Giessen (Germany)

Alkaline hydrolysis of phenyl hydrocinnamates, thiohydrocinnamates, and selenohydrocinnamates substituted in the phenolic or isologous group has been studied kinetically. It was shown that polar effects of the substituents are transferred uniformly over to the reaction centre (*viz.* the carbonyl atom) via the heteroatoms oxygen, sulfur, and selenium, in spite of their differing electronegativities and polarizabilities. This conclusion follows from the fact that the straight lines obtained on plotting the values of log k for the hydrolyses against Hammet's σ-constants are parallel. Deviations from the straight line of the points obtained for the values of log k for *p*-NO_2-substituted compounds suggests an almost equal resonance between the heteroatom and the phenyl residue for the O- and S-isologues; in the case of the Se-isologues, a slight decrease in the resonance is observed.

By applying a proportionality found by the author, between the carbonyl frequencies of isologous esters of this type and the σ-constants, the new findings may be used for rapid semiquantitative estimation of half-lives and rates of hydrolysis of isologous esters of type *(31)* where X = O, S, or Se, and R = alkyl, aralkyl, or aryl.



(31)

Trifluoromethylsulfenyl Isocyanate

A. Haas, Göttingen (Germany)

Interaction of F_3C–SCl and AgOCN in a sealed tube at room temperature yielded, in addition to F_3C–S–NCO, a second transparent colorless oily liquid, which was identified by hydrolysis and infrared investigations as *N,N*-bis(trifluoromethylsulfenyl)carbamoyl isocyanate [6].

In common with organic isocyanates, F_3CS–NCO is capable of adding on compounds with acidic hydrogen, yielding, for example, the new derivatives *(32)* and *(33)*.

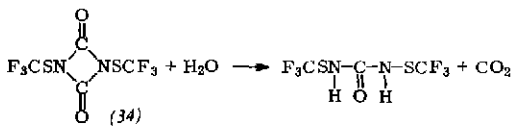
$$F_3CS{-}NCO \xrightarrow{ROH} F_3C{-}S{-}NHCOOR \quad (R = CH_3 \text{ or } C_3H_7) \qquad (32)$$

$$\xrightarrow[[(CH_3)_3Si]_2NH]{} F_3C{-}S{-}NHCON[Si(CH_3)_3]_2 \qquad (33)$$

[4] *J. Goerdeler* and *H. Horstmann*, Chem. Ber. *93*, 671 (1960).

Reaction of $(F_3CS)_2N-CO-NCO$ with methanol yields $(F_3CS)_2N-CO-NHCOOCH_3$, which was hydrolysed in boiling moist CS_2 to $F_3CS-NHCONH-COOCH_3$.

A cyclic dimer *(34)* is obtained in sealed tubes after 8 weeks at 20 °C or 1 hr at 100 °C. Compound *(34)* is bis(trifluoromethylsulfenyl)uretdione, as was confirmed by hydrolysis:



(34)

NMR measurements of this compound show a chemical shift of 50.8 ppm with respect to CCl_3F.

Trimeric $F_3C-S-NCO$, or tris(trifluoromethylsulfenyl) isocyanurate, is obtained most reliably by heating the monomer in a sealed tube in the presence of small quantities of anhydrous sodium acetate.

Notes on the Sakaguchi Reaction

A. Heesing, Münster/Westfalen (Germany)

The dyestuffs formed during the color reaction on monosubstituted guanidines discovered by *S. Sakaguchi* in 1925 were separated by chromatography and isolated in pure form. With alkyl-substituted guanidines, invariably only one dyestuff is formed whereas several components occur with guanidinoacetic acid and arginine. With guanidinoacetic acid, the main component is accompanied by secondary products which are due to esterification and ring closure during the process of isolation. Like the alkyl derivatives [7], the main dyestuff is a quinone imine, contrary to earlier proposed structures which were assumed to be similar to indophenol [8]. The products of alkaline disproportionation (2-bromo-1-naphthol and glycine) and the properties of the n-butyl ester correspond to this structure. In both the main components of the dyestuff mixture which is obtained from arginine, γ-guanidinobutyronitrile (resulting from decarboxylation and dehydrogenation of the arginine in the alkaline hypobromite solution) and arginine are present as side chains on the same skeleton since γ-aminobutyronitrile and ornithine are found on hydrolysis. By using substituted naphthols as well as naphthoquinones in place of the α-naphthol in the Sakaguchi reaction, it was made probable that direct substitution by guanidine of the bromine introduced into the *p*-position occurs.

Cyclic Phenylsilanes

E. Hengge, H. Reuter, and *R. Petzold*,
Marburg/Lahn (Germany)

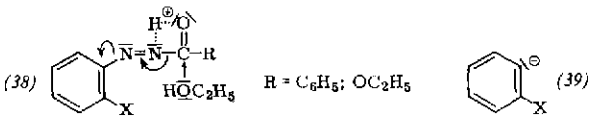
On treatment of diphenyldichlorosilane with sodium, two substances, *viz. (35)* and *(36)*, with overall composition $(Si(C_6H_5)_2)_n$ are formed which, according to *Kipping*, have n = 4, with Si_4-ring and -chain structures, respectively. *Gilman* assumed that *(36)* is an Si_6-ring and that *(35)* is an Si_4-ring but corrected his view to consider *(36)* as an Si_5-ring. Determinations of the molecular weights of *(35)* and *(36)* indicated that n = 4 in both cases, but the results are inaccurate because of poor solubilities and high molecular weights. On oxidizing *(35)* and *(36)*, the same product, *viz.* $Si_4(C_6H_5)_8O_2$ *(37)*, is formed from each compound. *(37)* can be synthetized from 1,3-dibromo-1,1,3,3-tetraphenyldisiloxane by a Wurtz synthesis, which establishes its structure as octaphenylcyclodioxahexasilane. Cleavage of *(35)* and *(36)* with Li followed by methylation gives two different dimethyloctaphenyltetrasilanes.

It was concluded from this that *(35)* and *(36)* are stereoisomeric phenylated Si_4-rings. It can be shown by means of a model that octaphenylcyclotetrasilane must be capable of existing in two forms that are not mutually interconvertible. In one case, the shielding effect of the phenyl groups is so strong as to account for the unreactive behaviour [of *(36)*], while in the other, the Si–Si bonds of the ring are accessible for attack by reagents, so that the observable scission [of *(35)*] with iodine can occur. The dihalide obtained, like the corresponding methyl compound, is constrained into a U-form by the bulky phenyl residues. It cannot undergo transition into a chain form which is also possible, so that the occurrence of two stereoisomeric dimethyloctaphenyltetrasilanes can be explained.

Heterolytic Fragmentation of Azo Compounds

Reinhard W. Hoffmann, Heidelberg (Germany)

Arylazocarbonyl compounds of type *(38)* are not only susceptible to base-catalysed fragmentation [9], but also disintegrate readily under the influence of acids. The products obtained make it likely that the *o*-halophenyl anion *(39)* is formed as an intermediate.



(38) R = C_6H_5; OC_2H_5 *(39)*

In alkaline (ethoxide) ethanolic medium loss of halogen ions from *(39)* yielding dehydrobenzene can compete (if X = Br or I, but not if X = Cl) with the protonation of *(39)* leading to a halobenzene. The ratio of the amount of products derived from dehydrobenzene to the amount of halobenzene formed allows to determine the relative rates for the loss of Br^- and I^- from *(39)* using diffusion-controlled protonation of *(39)* as an internal standard.

In an acidic ethanolic medium, on the other hand, protonation of *(39)* completely overshadows the elimination of halogen ions. It therefore appears that the fragmentation of azocarbonyl compounds is a mild method of generating carbanions without organometallic reagents.

Alkali Metal Oxomercurates(II)

R. Hoppe and *H. J. Röhrborn*,
Münster/Westfalen (Germany)

Mixtures of Li_2O, Na_2O_2, $KO_{0.63}$, $RbO_{0.85}$, or $CsO_{1.25}$ with HgO in the ratio M^I:Hg = 2:1 were heated to 250 °C in a sintered corundum boat in a glass ampoule. In every case, hitherto unknown compounds of the type M_2HgO_2 were formed. Single crystals of Na_2HgO_2 and K_2HgO_2 were obtained by tempering for 10 hours at 500 °C (quartz ampoule) and annealing for 100 hours at 350 °C.

These oxomercurates(II) are colorless and unusually sensitive to moisture. Even in petroleum dried over Na, they rapidly form yellow-orange to red hydrolysis products.

According to their powder diagrams, all the compounds crystallize in the body-centered tetragonal system.

Li_2HgO_2	$a_0 = 3.55$ Å	$c_0 = 11.22$ Å	$c/a = 3.16$
Na_2HgO_2	3.42	13.32	3.89
K_2HgO_2	3.92	13.94	3.56
Rb_2HgO_2	4.13	14.19	3.44
Cs_2HgO_2	4.35	14.51	3.34

[6] *H. J. Emeleus* and *A. Haas*, J. chem. Soc. (London) *1963*, 1272.

[7] *A. Heesing*, Chem. Ber. *95*, 3008 (1962).

[8] *W. R. Fearon*, Sci. Proc. Roy. Dublin Soc., Ser. A *22*, 415 (1941); *K. R. Bhattacharya, J. Datta* and *D. K. Roy*, J. org. Chemistry *25*, 2035 (1960).

[9] *R. W. Hoffmann*, Angew. Chem. *75*, 168 (1963); Angew. Chem. internat. Edit. *2*, 153 (1963).

The crystal structures of the isotypic compounds Na_2HgO_2 and K_2HgO_2 were determined using Fourier methods. They crystallize in the space group D_4^9-I42 with 2 Hg in 2(a), 4 Na or 4 K in 4(e) with $z_{Na} = 0.325$ or $z_K = 0.331$, and 4 O in 4(e) with $z_O = 0.147$ (Na_2HgO_2) or $z_O = 0.138$ (K_2HgO_2). The structure is well-defined [Na_2HgO_2: 80 reflexions (h0l), $R = R' = 7.8\%$; K_2HgO_2: 62 reflexions (h0l), $R = R' = 7.7\%$; Mo-K-radiation, absorption taken into account]. Rotating crystal, Weissenberg, precession, and Laue photographs were taken at [100] and [001]. Rb_2HgO_2 and Cs_2HgO_2, but not Li_2HgO_2, probably crystallize with the same type of structure.

The linear structural group $[HgO_2]^{2-}$ is the most important structural element, with Hg–O = 1.96 Å (Na_2HgO_2) or 1.93 Å (K_2HgO_2). Na and K are surrounded by five oxygen atoms (tetragonal pyramid).

Preparation of Well-Defined Polyniobates by Hydrolysis of Pentaethyl Niobate

K. F. Jahr, *J. Fuchs*, and *G. Heller*, Berlin (Germany)

A condensation process is superimposed on the hydrolysis of some inorganic esters when these are dissolved in an organic medium. The resulting intermediate polyanions can be "fixed" by salt formation if a suitable base is present. In this way, definite polyniobates can be obtained by saponification of pentaethyl niobate. Both the degree of condensation of the polyanions and the base-acid ratio in the salts are determined essentially by the pK value of the base present. In a suitable solvent, reaction (b) proceeds quantitatively in favor of salt formation.

$$\text{Inorganic ester} + \text{base} + \text{water} = \text{salt} + \text{alcohol} \qquad \text{(b)}$$

If the ester and base are in excess, then the water available is used up quantitatively.

Analytical determination of the base-acid ratio of the products together with measurement of the water uptake confirmed the formation of polyniobates containing the anions:

$Nb_6O_{19}^{8-}$, $H_6Nb_{12}O_{37}^{8-}$, $H_8Nb_{12}O_{37}^{6-}$, $H_9Nb_{12}O_{37}^{5-}$, and $Nb_{24}O_{65}^{10-}$

All the compounds prepared according to (b) are, in practice, free of water of crystallization. If for reasons of crystal chemistry, solvent molecules must be included, organic solvent is absorbed to form solvated ions.

This method of preparation is useful for the production of easily hydrolysed substances that are hence not obtainable from aqueous solution. For example, polyniobates of weak organic bases as well as the ammonium salt were thus obtained for the first time. Since the products contain no water of crystallization, their water of constitution can be determined easily from the water content after hydrolysis. From this data, information concerning the composition of the polyanions in solution can be obtained.

Nucleophilic Behavior of Diphenylcarbene

W. Kirmse, Marburg/Lahn (Germany)

Carbenes and secondary carbonium ions formally exist in an acid-base relationship:

$$R_2C: + H^{\oplus} \rightleftharpoons R_2CH^{\oplus}$$

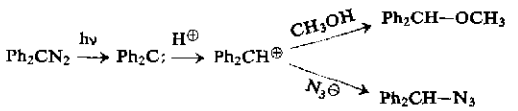
Experimental indication of such a relationship has hitherto been given only by carbenes with α-nitrogen atoms, which, by reason of their mesomerism, are closely related to isonitriles [11].

We were able to show that diphenylcarbene, which is produced by photolysis of diphenyldiazomethane, adds on a proton in alcohols to give the diphenylcarbonium ion.

[11] *H. W. Wanzlick*, Angew. Chem. *74*, 129 (1962); Angew. Chem. internat. Edit. *1*, 75 (1963).

Experiments allowing competitive reaction with oxygen afford proof of the nucleophilic character of diphenylcarbene: whereas alcohols effectively prevent autoxidation of diphenylcarbene, amines and nucleophilic anions have no such effect. The activity of the alcohols increases with their acidity, and their effect must therefore involve protonation of the diphenylcarbene. (Protonation of diphenyldiazomethane in the activated state is ruled out by measurements of the quantum yield).

Photolysis of diphenyldiazomethane in a methanolic solution of lithium azide affords benzhydryl methyl ether and benzhydryl azide in about the same proportions as solvolysis of benzhydryl chloride does. This proves that the diphenylcarbonium ion must be an intermediate:



Diphenylenecarbene (prepared from diazofluorene) has considerably weaker nucleophilic reactivity.

Selectivity of Alkalized Iron Catalysts

H. Kölbel, *W. K. H. Müller*, *E. Schöttle*, and *H. Hammer*, Berlin (Germany)

Investigations of the change in electronic work function of iron films impregnated with K_2CO_3 (as analogues for alkalized iron catalysts) on chemisorption of CO and H_2, measurements of the change in electrical conductivity of iron films formed by vaporization *in vacuo*, onto which potassium had been condensed, and microcalorimetric measurements of the heat of chemisorption of CO on alkalized, precipitated iron catalysts have led to the following conclusions:

1. During chemisorption of CO on Fe, metal electrons are displaced towards the CO.

2. The alkali promoter, which donates electrons easily to the system, facilitates the formation of electron-accepting CO-adsorbates.

3. The metal-carbon bond is strengthened by the promoter.

4. Chemisorption of H_2, which appears to proceed with electron transfer to the metal if the coverage is greater than monomolecular, is strongly inhibited by the promoter.

Attempts were made to draw conclusions from these observations on the individual steps of the reaction mechanism proposed by *Storch*, *Golumbic*, and *Anderson* for the Fischer-Tropsch synthesis, particularly with respect to the termination reactions. The familiar fact that alkali influences the selectivity of the catalysts resulting in a greater yield of olefins and oxygenated aliphatic compounds as well as in a higher mean molecular weight of hydrocarbons was shown qualitatively to be due to electronic interaction between the catalyst metal, the chemisorbed reactants, and the alkali promoter.

Dipole Moments and Magnetic Properties of Several Metal Complexes of Dialkyldithiophosphinic Acids

W. Kuchen and *A. Judat*, Aachen (Germany)

Complexes *(40)* were obtained on reaction of sodium diethyldithiophosphinate with $SnCl_4$ or diorganochlorostannanes in benzene according to (c).

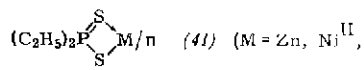
$$2(C_2H_5)_2P(S)SNa + R_2SnCl_2 \rightarrow [(C_2H_5)_2PS_2]_2SnR_2 + 2\ NaCl \qquad \text{(c)}$$
(40)

($R = Cl$, C_6H_5, C_4H_9)

By assuming an octahedral structure (the dichloro compound proved to be a non-electrolyte in dimethylformamide), a *cis*- or *trans*-form became possible for *(40)*.

Dipole measurements gave moments of considerable magnitude for *(40)* (R = Cl: 7.63; R = C_6H_5: 3.32; R = C_4H_9: 3.22 D); this leads to the conclusion that the configuration is *cis*.

Dipole moments between 1.2 and 1.9 D were also found for *(41)*, *i.e.* values comparable to those of metal acetylacetonates



(41) (M = Zn, Ni^{II}, Co^{II}, Pb^{II}, Cr^{III} etc.)

and other non-electrolyte coordination complexes. It is assumed that, like the metal acetylacetonates, the compounds *(41)* do not possess a permanent dipole and that the moment observed is to be ascribed to an abnormally high atomic polarization, as again applies to the acetylacetonates. Calculation of P_A from $P_M = P_O + P_E + P_A$ with $P_O = 0$ showed that in the Pb- and Bi-complex, the atomic polarization amounts to more than 50 % of the electronic polarization. The P_A values of *(41)* are consequently of approximately the same order of magnitude as the atomic polarizations determined by *Coop* and *Sutton* (1938) for the acetylacetonates.

Magnetic investigations of *(41)* gave a magnetic moment for the violet Cr(III) complex which corresponded almost exactly to the value of 3.87 Bohr magnetons calculated for three unpaired electrons. A Curie-Weiss constant Θ of only a few degrees was also obtained. Values of $\mu = 4.82$ Bohr magnetons and $\Theta \approx -49\,^\circ$ were found for the emerald-green Co(II) complex. The tetrahedral structure of the complex follows from this evidence and on the basis of the coordination number 4 for the complex, which is soluble in benzene in monomeric form. The blue-violet Ni(II) complex is diamagnetic and reacts with pyridine and thiophene to give pale green $[(C_2H_5)_2PS_2]_2NiPy_2$ and indigo-blue $[(C_2H_5)_2PS_2]_2Ni(C_4H_4S)_2$. Both adducts are extremely labile and quickly revert to the original complex in air. The Ni complex reacts with dry NH_3, binding $6\,NH_3$ to give lilac $[Ni(NH_3)_6][(C_2H_5)_2PS_2]_2$.

Carbonyl Olefination

H. Machleidt, V. Hartmann, G. Strehlke, and *R. Wessendorf*, Bonn (Germany)

Wittig compounds (*i.e.* ylides) containing resonance-stabilizing groups do not react with ketones. Chloro or fluoro substituents in the ketone, however, facilitate olefin formation with triphenylethoxycarbonylmethylenephosphorane. According to *H. J. Bestmann*, *C*-alkylation of the ylide is made possible by bromo and iodo substituents.

PO-Activated olefination by the carbanion of ethoxycarbonylmethylphosphonic ester *(42)* results in higher yields in the olefination of the halogeno ketones; only iodoacetone undergoes *C*-alkylation. The resonance-stabilized carbanion of acetonylphosphonic ester reacts to a lesser extent with carbonyl compounds to yield α,β-unsaturated ketones. A fluoro substituent in the ketone again increases the yield of olefin, while stabilization of *(42)* by an additional ethoxycarbonyl or acetyl group results in decreased olefin production. The only carbonyl component that underwent reaction was benzaldehyde.

Olefin formation is obviously controlled by the stability of an intermediate which exists in equilibrium with the carbonyl component and the carbanion. The presence of fluorine and other electrophilic substituents in the carbonyl compound retards charge separation, thus leading to olefin formation. Parallel principles apply to the Michaelis-Arbusow reaction and to the Perkow reaction. With increasing mobility of the halogen, *i.e.* Cl > Br > I, halogenated ketones react according to the Arbusow reaction (*i.e.* nucleophilic substitution of the C-halogen bond). Substitution by fluorine, however, promotes exclusively the Perkow reaction, which involves attack of triethyl phosphite on the carbonyl group of the halogeno ketone. 1-Iodo-3-fluoroacetone gave the enol-phosphate ester of fluoroacetone in quantitative yield.

Dialkyls and Diaryls of Tin and Germanium

W. P. Neumann, Giessen (Germany)

Cyclic oligomers of dialkyltin (R = C_2H_5, C_6H_5) are obtained by catalytic elimination of hydrogen from dialkyltin dihydrides [12] according to (d):

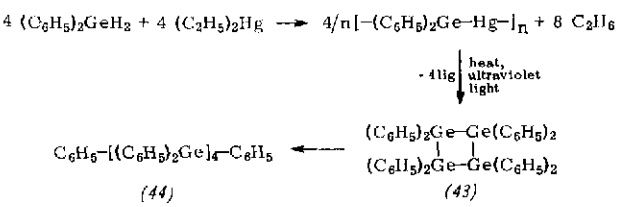
$$n\,R_2SnH_2 \xrightarrow{\text{cat.}} n\,H_2 + (R_2Sn)_n \qquad (d)$$

It has now proved possible to prepare crystalline compounds with R = $CH_2CH(CH_3)_2$, C_2H_5 (n = 9), β-naphthyl (n = 6), α-naphthyl, and *p*-biphenylyl (n still unknown) by the same means. Under other conditions, hexameric diisobutyltin was formed. An organometallic complex compound, e.g.

$$(C_2H_5)_2SnCl_2 \cdot 2\,C_5H_5N,$$

was used as catalyst in (d).

Oligomeric silicon and germanium dialkyls could not be prepared according to (d) [13] but, by contrast, a crystalline cyclic tetramer of diphenylgermanium *(43)* [14, 15] was obtained in good yield from the dihydride as follows:



(44) *(43)*

Compound *(43)* crystallizes from benzene, m.p. 238 °C (partial decomp.), is stable in air, and is converted into crystalline decaphenyltetragermane *(44)* by iodine and phenyl-lithium or alternatively by lithium and bromobenzene. The synthesis leading to *(43)* can be applied to aliphatic germanium dialkyls. When $(C_6H_5)_2GeCl_2$ is treated with finely divided lithium in tetrahydrofuran, a resin is formed together with pentameric and hexameric diphenylgermanium; the former is readily soluble in benzene and is precipitable with ether, the latter is only sparingly soluble in benzene. Both compounds are cyclic and give well-formed crystals in net yields of 33 % and 3 %, resp. The molecular weights were determined almost exclusively with a vapour pressure osmometer.

Monosaccharides Containing Nitrogen in the Hemiacetal Ring

H. Paulsen, Hamburg (Germany)

With 5-amino-sugars, cyclization to form a hemiacetal involves a competing reaction between the amino and a hydroxy group, thus yielding either a piperidinose form (containing nitrogen in the hemiacetal ring), or a furanose form. A series of 5-amino-sugars were synthetized and their tendency to cyclize examined.

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[12] *W. P. Neumann*, Angew. Chem. *74*, 122 (1962); *W. P. Neumann* and *K. König*, Angew. Chem. *74*, 215 (1962); Angew. Chem. internat. Edit. *1*, 212 (1962).

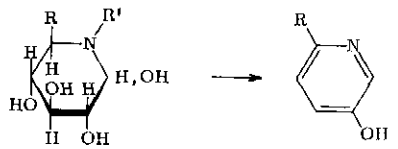
[13] *F. Glockling* and *K. A. Hooton*, J. chem. Soc. (London) *1963*, 1849, recently reported failure of the synthesis with diphenylgermanium dihydride.

[14] We express our gratitude to the Germanium Research Committee and to Prof. *G. J. M. van der Kerk*, Utrecht (Holland) for the valuable starting material.

[15] A tetrameric diphenylgermanium was first described by *C. A. Kraus* and *C. L. Brown*, J. Amer. chem. Soc. *52*, 4031 (1930).

5,6-Diacetamido-5,6-dideoxyhexoses yield preferentially furanose forms. 5,6-Diamino-5,6-dideoxyhexoses yield an intermediate piperidinose *(45)*, which is converted, with elimination of 3 moles of water, into 5-aminomethyl-3-hydroxypyridine *(49)*. The piperidinose *(46)* derived from 5-amino-5,6-dideoxy-6-nitrohexoses yields *(50)* similarly with loss of water. It is assumed that the elimination of water proceeds primarily via a Δ^1-piperideine.

5-Acetamido-5-deoxy-D-xylose yields a stable crystalline piperidinose *(47)*, together with the corresponding furanose. 5-Amino-5-deoxy-D-xylose, when liberated hydrolytically, affords the piperidinose *(48)* as an intermediate which is converted spontaneously into 3-hydroxypyridine *(51)*.



(45) R = CH_2NH_2; R' = H
(46) R = CH_2NO_2; R' = H
(47) R = H; R' = $COCH_3$
(48) R = R' = H

(49) R = CH_2NH_2
(50) R = CH_2NO_2
(51) R = H

The results of these experiments permit the following two conclusions. 5-Acylamido-sugars may give rise to stable piperidinose forms in addition to the normal furanose forms, provided that this process is favored by the configuration, the conformation, and the reactivity of the acylamido group. 5-Amino-sugars containing a free primary amino group yield piperidinose forms as intermediates which lose 3 moles of water spontaneously in acid solution, yielding 3-hydroxypyridine derivatives.

Some Mercury Chalkonium Compounds

H. Puff, Kiel (Germany)

Of the compounds $Hg_3Y_2X_2$, where Y = S, Se, or Te and X = Cl, Br, or I [18], $Hg_3S_2Cl_2$ [19], $Hg_3Se_2Cl_2$, $Hg_3Te_2Cl_2$, and $Hg_3Te_2Br_2$ crystallize in the cubic [20], $Hg_3Se_2Br_2$ in the rhombic, and $Hg_3Te_2I_2$ in the monoclinic system [18]. The positive charges of a polycation with bivalent Hg and trivalent chalkogen, *viz.* the structural group ($Hg_3X_2^{++}$), is compensated by isolated halide ions. Analogous structures are possessed by:

$Hg_3S_2Br_2$	rhomb.	a = 9.24	b = 18.36	c = 9.11 Å	Z = 8
$Hg_3S_2I_2$	rhomb.	9.78	18.68	9.43	8.

The cubic compounds, whose occurrence is associated with a fixed ratio of the cationic structural group's radius to the anionic radius, form mixed crystals, as does $Hg_3Se_2Cl_2$ with $Hg_3Se_2Br_2$; this latter series is still incomplete, however. The chalkogen-Hg-chalkogen angle differs from 180° and is due to a weak bond between the Hg and halogen and a resulting slight sp^3 hybridization, in accordance with the observed shortening of the interatomic distance.

Other compounds of this type include: $Hg_3S_2SO_4$, colorless, hexagonal, a = 7.10 Å, c = 8.25 Å, z = 2; $Hg_3Se_2SO_4$, colorless; $Hg_3Te(SO_4)_2$, yellow, cubic, a = 10.07 Å, z = 4, probable formula $Hg_3Te_2SO_4 \cdot 3HgSO_4$; $Hg_3S_2(ClO_4)_2$, colorless, hexagonal, a = 7.15 Å, c = 17.0 Å, z = 3, explosive.

The compounds of the hexagonal group cannot, as is usually possible within a group, be converted into compounds of the cubic group by exchange of anions. This can be explained as being due to a basically different type of cationic structure.

[18] *H. Puff* and *R. Kohlschmidt*, Naturwissenschaften *49*, 299 (1962).

[19] *H. Puff* and *J. Küster*, Naturwissenschaften *49*, 299 (1962).

[20] *H. Puff* and *J. Küster*, Naturwissenschaften *49*, 464 (1962).

Results of Electron-probe Microanalysis Investigations

A. Rabenau, Aachen (Germany)

The electron beam of the X-ray microanalyser [21] can scan any surface area of a specimen up to 400×400 μ^2 and produce an X-ray image of this section, which shows the distribution of any selected element with an atomic number between 12 and 92. It is also possible to scan any selected line across this surface and record the variation of the X-ray intensity.

With this technique the phase relationships in the binary system Bi–Te could be clarified. This system includes the compound Bi_2Te_3 which recently has been of considerable interest, particularly as a thermoelectric material. In thermal equilibrium Bi_2Te_3 dissolves Bi to a great extend; the phase boundary at RT lies between 52.2 and 55 atom-% Bi. It thus includes the composition of the mineral wehrlite, ≈ BiTe. This was also confirmed by locating the solidus in this region. The solubility of Te in Bi_2Te_3 however is less than 1 atom-%. There exists still another phase in the system including the composition Bi_2Te, which is found in nature as the mineral hedleyite (*Deneke*, *Ober*).

The influence of small quantities (< 1 % by weight) of nickel and manganese on the sintering behavior and on the grain growth of TaC during hot pressing was investigated, and the distribution and solubility of this metals was determined. The solubilities of manganese and nickel in TaC hot pressed at 2600 °C and 300 kg/cm² are about 2 atom-% and about 0.2 atom-%, respectively (*Roeder*, *Klerk*) [22].

The Systems NiO-VO and MgO-VO

B. Reuter and *K. Jaeger*, Berlin (Germany)

The two oxides NiO and VO, which crystallize with the NaCl structure, do not form mixed crystals *in vacuo*, despite their similarity of lattice parameters. Instead, the NiO is reduced to the metal above 700 °C, analogous to FeO and CoO, while in the presence of sufficient NiO, the VO is oxidized to the upper phase boundary of V_2O_3 (about $VO_{1.55}$).

Similarly, no mixed crystals are formed in the system MgO–VO. Between 800 and 1050 °C, the VO disproportionates in the presence of the MgO to yield V and V_2O_3, which immediately reacts further with the MgO to form a magnesium vanadium(III) spinel MgV_2O_4. Hence an equimolar mixture of V and MgV_2O_4 results, together with some excess MgO or VO.

Although Mg reduces higher vanadium oxides to metallic vanadium below 1050 °C, at higher temperatures, the reduction stops at the upper phase boundary of VO ($VO_{1.2}$). Conversely, above 1050 °C, V reduces the MgO to the metal, which vaporizes, and $VO_{1.2}$ is formed. First, free MgO is attacked and only then the MgV_2O_4, resulting in a pronounced MgO deficiency in the spinel. However, MgO is no longer able to reduce VO but it can perhaps reduce some of the V^{3+} in the spinel to V^{2+}, which in turn is reoxidized to $VO_{1.2}$. In this way, in the system MgO–VO at temperatures above 1050 °C, depending on the proportions, the products are a more or less indefinite Mg–V spinel, $VO_{1.2}$, and metallic magnesium, together with some excess MgO. The insensitivity of the spinel phase to MgO deficiency and reduction is noteworthy, as is also the unusual stability of the upper boundary of the VO phase.

Thermal Rearrangement of Bicyclo[6,1,0]nona-2,4-diene

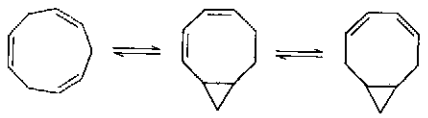
W. Roth, Köln (Germany)

At 160 °C, bicyclo[6.1.0]nona-2,4-diene *(52)*, which is prepared by a CuCl-catalysed reaction of diazomethane with 1,3,5-cyclooctatriene, is in dynamic equilibrium with 1,4,7-cyclononatriene *(53)* and bicyclo[6.1.0]nona-3,5-diene *(54)*.

[21] Microscan, made by Cambridge Instrument Co. Ltd.

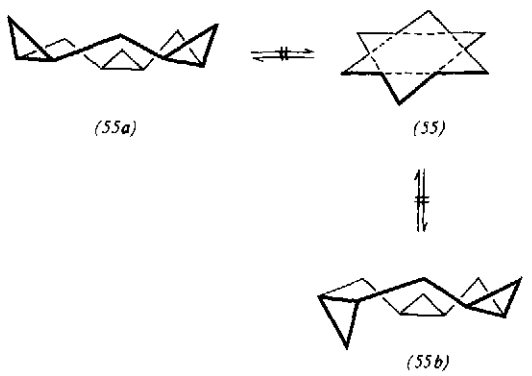
22] Z. Metallkunde, in the press.

In view of the small differences in free energy of the components, no significant homoaromatic stabilization can exist in *(53)*.



(53) (93%) *(52)* (6%) *(54)* (1%)

Reaction of *(53)* with diazomethane with CuCl as catalyst affords, in addition to other products, two isomeric hexahomobenzenes, with *cis,cis,cis*- and *cis,cis,trans*-cyclopropane rings *(55a)* and *(55b)*, respectively. The existence of two



(55a) *(55)* *(55b)*

stable geometric isomers which are not interconvertible, even at 400 °C, rules out a nonclassical structure *(55)* for hexahomobenzene [23], even under extreme conditions.

A New Method of Titration

B. Sansoni, Marburg/Lahn (Germany)

Equal volumes of a suitable homogeneous ion-exchange material under comparable conditions contain equal numbers of exchangeable groups or counter-ions. Hence beads of ion-exchange material of equal size always bind the same number of ions. These can be displaced quantitatively into the surrounding solution by concentrated solutions of neutral salts. Hence, ions may be added to a solution by binding them on a suitable ion-exchange material of uniform particle size and by counting out particles and eluting them.

For application to titration, the quantity of reagent used is calculated from the number of titrator-beads required to reach the end-point. In other words, the volume measurements of volumetric titration, the weight measurements of gravimetric titration, or the current measurements of coulometric titration is replaced by the enumeration of particles. The method can therefore be termed "numerometry", from the Latin *numerare*, to count [24]. Application of the method is not confined to the use of ion-exchange materials, but can readily be applied with other solid reagents in the form of sufficiently uniform beads (*e.g.* Na_2O_2) or particles of other shapes.

Using a counting rod, 1000 beads can be counted to within ± 0.3 % error in 7 min; 100 beads with ionic contents from 3 µequiv. to 0.22 equiv. permit a 10^5-fold range of application, from the ultramicro to full macro scale.

Titration of 10 mg of H_2SO_4 with OH^--Permutit ES (0.75 to 1.0 mm) gave relative standard deviation of ± 0.9 %; 490 mg of H_2SO_4 with beads of Na_2O_2 (0.5–0.6 mm), ± 0.75 %; 50 g of H_2SO_4 with NaOH pellets, ± 0.8 %; 1.2 mg of NaOH with H^+-Dowex 50 WX2 (0.20–0.25 mm), ± 1.6 %; 16 mg of NaOH with H^+-Lewatit S 100 (0.9–1.1 mm), ± 0.9 %; 15.5 mg of Fe^{3+} with H^+-Lewatit S 100 (0.6–0.75 mm), ± 2.4 %; and 25 µg of Cu^{2+} with Dowex 50 WX2 (0.20–0.25 mm), ± 16 %.

The accuracy and rapidity of volumetric measurements is not attained. However, there are substantial advantages, namely, the elimination of burettes and standard solutions; complete independence of room temperature, permitting the simple titration of melts; the small volume and superior titre-constancy of the solid titrator-beads; and finally, the avoidance of dilution during the titration.

[23] *S. Winstein* and *J. Sonnenberg*, J. Amer. chem. Soc. *83*, 3235, 3244 (1961); *R. S. Boikess* and *S. Winstein*, ibid. *85*, 343 (1963).

A Tungsten-Hydrogen Compound

Brigitte Sarry and *M. Dettke*, Berlin (Germany) [25]

Solutions in benzene of $W(C_6H_5)_4(LiC_6H_5)_2 \cdot 3(C_2H_5)_2O$ *(56)* take up $2H_2$ per W even under normal conditions. On adding cyclohexane to the solution, the reaction product is precipitated and can be isolated in a pure state as a black, pyrophoric powder, which is extremely sensitive to hydrolysis and which has the composition $WH(LiC_6H_5)_2$ *(57)*. LiH is not formed during the hydrogenation.

The formula of *(57)* was established as follows:

Hydride hydrogen: 1 H is evolved on protolysis and on thermal decomposition up to 200 °C. Above 245 °C a second evolution of hydrogen occurs which is caused by cracking of the organic residue.

Phenyl: In a very carefully conducted protolysis, the phenyl residue is eliminated quantitatively as benzene. 2 C_6H_6 per molecule are found by gas chromatography.

Li: On acidimetric titration, the strongly alkaline hydrolysis solution, shows pH discontinuities at 2 and 3 equivalents of acid. They correspond to the neutralization of LiOH and WOH, respectively. The flame-photometric estimation also gives 2 Li.

Compound *(57)* is diamagnetic, which indicates that the spins are paired by dimerization. When the compound is isolated in a solid state, it becomes insoluble; this points to an even higher degree of polymerization.

Solutions of *(56)* in ether also absorb H_2, but in a stepwise manner. At first 1 H_2 is taken up reproducibly and then, after a fairly long time, up to 1.5 H_2 is consumed irreproducibly in a second reaction. From this it is concluded that the course of the hydrogenation is a follows:

1st stage (in C_6H_6 and ether):

$$(56) + H_2 \rightarrow WH(C_6H_5)_3(LiC_6H_5)_2 + C_6H_6$$

2nd stage a) (in C_6H_6):

$$WH(C_6H_5)_3(LiC_6H_5)_2 + H_2 \rightarrow (57) + 2\,C_6H_6 + {}^1/_2\,(C_6H_5)_2$$

b) (in ether):

$$WH(C_6H_5)_3(LiC_6H_5)_2 + x\,H_2 \rightarrow (57) + 2x\,C_6H_6 + \frac{3-2x}{2}\,(C_6H_5)_2$$

(where $0 \leqslant x \leqslant 3/2$).

Conductometric Titrations in Liquid Ammonia

P. W. Schenk, *K. Huste*, and *E. Tulhoff*, Berlin (Germany)

A titration apparatus for working with liquefied gases, and its use in conductometric titrations with potassamide in liquid ammonia were described. Some solvolysis reactions were investigated, including those of tetrasulfur tetra-imide, tetrasulfur tetranitride, and of some sulfur halides. In the case of $S_4N_4H_4$, the titration curves showed sharp points of inflection at 1, 2, 3, 4, 5, and 8 moles of KNH_2 per $S_4N_4H_4$, which permit conclusions as to the course of solvolysis, which leads to $S(NHK)_2$, a compound previously described by *Meuwsen*. With S_4N_4, points of inflection were found at 2, 4, and 6 moles of KNH_2/S_4N_4. These correspond to solvolysis according to the scheme originally proposed by *Ruff* and *Geisel* and later confirmed by *Becke-Goehring* et al.

[24] Thanks are accorded to Prof. *Rancke-Madsen*, Copenhagen, for discussions.

[25] *H. Grossmann* collaborated in the experimental work.

Investigation of ammonolysis of the halides of Zn, Cd, Hg, V, Ti, Mn, and Ce showed that Zn and Cd form amides and amidometallates. Similar titration curves were given by $HgCl_2$. With VBr_3, the first point of inflection corresponds to the known compound VBr_2NH_2; other inflections indicate formation of the imide $VNHNH_2$ (or $V_2(NH)_3$) and of potassium vanadium(III) imide. $TiCl_4$ shows a first inflection corresponding to $TiCl(NH_2)_3$ or $TiClNHNH_2$. VCl_4 gave VCl_2NH. Other points of inflection indicated amides or imides and imido- or amidometallates. With Mn^{4+} and Ce^{4+}, several solvolysis products of varying halogen content were observed.

The Octamethyldisiloxalanate Anion, an Isoster of Octamethyltrisiloxane

H. Schmidbaur, Marburg (Germany)

Sodium or potassium trimethylsilanolate cleaves the four-membered ring system of bis-pentamethylsiloxalane [26] in an exothermic reaction even at room temperature. Well-formed crystals of sodium *(58)* or potassium octamethyldisiloxalanate *(59)*, respectively, separate out in good yields from inert organic solvents. Special bonding conditions must be ascribed to the anion because of its isosterism with the uncharged compound octamethyltrisiloxane *(60)*. The formation of an entirely $d_\pi p_\pi$-stabilized Si–O–Al–O–Si skeleton imparts unusual properties to the new compounds.

(58) $Na[(CH_3)_3SiOAl(CH_3)_2OSi(CH_3)_3]$

(60) $(CH_3)_3SiOSi(CH_3)_2OSi(CH_3)_3$

Compounds *(58)*, m.p. 215 °C, and *(59)*, m.p. 125 °C, dissolve quickly and without decomposition in water and are only slowly hydrolysed with formation of CH_4, NaOH, $Al(OH)_3$, and $(CH_3)_3SiOH$. The NMR spectra of their aqueous solutions show the expected two proton signals, with an area ratio of 3:1 and $\Delta\nu = 1.30$ ppm. According to molecular-weight determinations in boiling benzene, *(58)* is monomeric and *(59)* is dimeric. The considerable differences in solubility of the salts in organic solvents and the characteristic distinctions in their infrared spectra indicate a fundamental difference in the co-ordination of the alkali metals to the anion. Both *(58)* and *(59)* cannot be sublimed and disintegrate rapidly in moist air. In acidic aqueous solution, they are hydrolysed instantly [27].

Structure of Halides and Oxyhalides of Nb and Mo

H. G. Schnering and *H. Wöhrle*,
Münster/Westfalen (Germany)

To lead to a better understanding of the breadths of the phases of $NbCl_3$ [28] and of the formation of $NbCl_3/NbOCl_2$ mixed crystals [29], the crystal structures of Nb_3Cl_8, $NbCl_4$, $MoCl_3$, $NbOCl_2$, $NbOI_2$, and $MoOCl_2$ were determined. Marked imperfections and twinning made the investigations difficult. $NbCl_4$ has a fibrous structure while all the other compounds exhibit layer lattices of similar construction.

In principle, all the structures involve closest packing of the anion, the metal atoms (M) being situated in the octahedral spaces. In all cases, the predominant characteristic is a considerable shortening of the M-M distances (2.78; 3.06; 2.76; 3.14; 3.16; 2.96 Å), which indicates M-M bonding. In Nb_3Cl_8, there are even Nb_3 groups (cf. $Zn_2Mo_3O_8$ [31]). The theory that σ-type bonds are formed by overlapping of d-orbitals of neighboring M particles is supported by the observation that M-M pairs are formed only when they share a common octahedron edge and not an octahedron surface (TiI_3 type [32]). The anomalous magnetic properties of the compounds can be understood on this basis (Nb_3Cl_8: 1.83 Bohr magnetons per mole; $NbCl_4$, $NbOCl_2$, $NbOI_2$: non-magnetic; $MoCl_3$, $MoOCl_2$: μ_{eff} between 0.30 and 0.50) – particularly the marked difference between $MoCl_3$ and $MoBr_3$ (TiI_3 type) [33]. From the metric comparisons of Nb_3Cl_8, $NbCl_4$, and $NbOCl_2$, conclusions can be drawn concerning the structural elements in the $NbCl_3$ phase and in $NbCl_3/NbOCl_2$ mixed crystals. By consideration of extensive model calculations, the phase "$NbCl_3$" can be thought of as a limited $Nb_3Cl_8/NbCl_4$ mixed crystal region.

				a [Å]	b [Å]	c [Å]	β [°]
Nb_3Cl_8 [30]	green	hexagonal	$P\bar{3}m1$	6.744	–	12.27	–
$NbCl_4$	brown	monoclinic	C2/m	12.32	6.82	8.21	134
$MoCl_3$	black	monoclinic	C2/m	6.065	9.76	7.25	124
$NbOCl_2$	black	monoclinic	C2	12.79	3.93	6.70	105
$NbOI_2$	black	monoclinic	C2	15.08	3.92	7.48	105
$MoOCl_2$	yellow	monoclinic	C2/m	12.77	3.76	6.54	105

Alkali Chloride-Chromous Chloride Systems

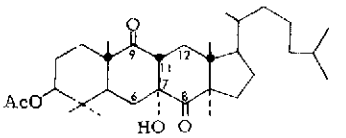
H. J. Seifert, Giessen (Germany)

The phase diagrams of the systems alkali chloride–chromous chloride were determined by means of differential thermal analysis. With potassium, rubidium, and cesium chlorides, chromous chloride forms two compounds each, these being of the type M_2CrCl_4 and $MCrCl_3$ and melting congruently – with the exception of Cs_2CrCl_4. The only compound occurring in the system $NaCl–CrCl_2$ is Na_3CrCl_5, which melts incongruently. $CrCl_2$ is soluble in LiCl up to 40 mole-%. The mixed crystals decompose at low temperature. Solubility of LiCl in $CrCl_2$ could not be detected. The compounds of the type $MCrCl_3$ crystallize with perovskite-like structures. Their stability decreases from the Cs to the K compounds owing to the increasing difference between the ionic radii of the chloride and alkali ions. In contrast to $CsCuCl_3$ and the binary chromous halides, all the $Cr^{2+}–Cl^-$ distances in $CsCrCl_3$ are equal. The coordination number of chromium in Cs_2CrCl_4 is 6, but it displays tetrahedral coordination in the analogous Cu compound. The differences in the polarizing effect of the transition metal ions may be responsible for this change.

Preparation of Linearly Anellized Steroid Analogues from Lanosterol

G. Snatzke, *A. Nisar*, and *H.-W. Fehlhaber*, Bonn (Germany)

3β-Acetoxy-Δ^8-lanostene is split by RuO_4 into the 8,9-seco-8,9-diketone, which on condensation with HCl in glacial acetic acid gives a B-nor-C-homo derivative. Repeated rupture of the double bond with RuO_4 yields an 8,9-seco-7,8,9-triketone, which can also be obtained from 3β-acetoxy-Δ^8-lanosten-7-one and which is very easily convertible into the 8(9→11)9(8→7)-diabeo-3β-acetoxy-7α-hydroxy-lanostane-8,9-dione *(61)*.



(61)

[26] *H. Schmidbaur* and *M. Schmidt*, J. Amer. chem. Soc. *84*, 1069 (1962).

[27] See also *H. Schmidbaur* and *M. Schmidt*, Angew. Chem. *74*, 589 (1962); Angew. Chem. internat. Edit. *1*, 549 (1962); *H. Schmidbaur*, Angew. Chem. *75*, 137 (1963); Angew. Chem. internat. Edit. *2*, 94 (1963).

[28] *H. Schäfer* and *K. D. Dohmann*, Z. anorg. allg. Chem. *300*, 1 (1959).

[29] *H. Schäfer*, *E. Sibbing*, and *R. Gerken*, Z. anorg. allg. Chem. *307*, 163 (1961).

[30] *H. G. v. Schnering*, *H. Wöhrle*, and *H. Schäfer*, Naturwissenschaften *48*, 159 (1961).

[31] *W. H. McCarroll*, *L. Katz*, and *R. Ward*, J. Amer. chem. Soc. *79*, 5410 (1957).

[32] *E. Holze*, Ph.D.Thesis, Universität Münster, 1957; *H. G. Schnering*, unpublished results.

[33] *D. Babel*, personal communication.

The 7α-position of the hydroxyl follows from the infrared spectrum (no H-bridge to the neighboring ketone). With thionyl chloride in pyridine, a smooth reaction takes place to give the Δ^6-ene-8,9-dione, which can be rearranged by treatment with HCl in acetic acid to the fully conjugated $\Delta^{7(11)}$-ene-8,9-dione. The double bond in this compound can be reduced with zinc in acetic acid.

Preparation of Silyl Azides [34]

W. Sundermeyer, Göttingen (Germany)

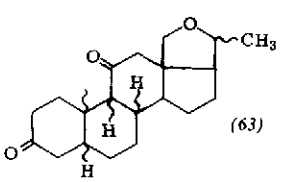
A series of organoazidosilanes $R_xSi(N_3)_{4-x}$ (R = CH_3, C_6H_5; x = 3,2,1) has been prepared in two ways: a) reaction of methylchlorosilanes with sodium azide in molten salts as solvent; b) reaction of preformed trimethylazidosilane with organochlorosilanes in the presence of aluminum chloride as catalyst (substituent exchange).

Furthermore, it proved possible to obtain the mixed halogene-pseudohalogeno-substituted organosilanes $CH_3SiCl_2N_3$, $CH_3SiCl(N_3)_2$, and $(CH_3)_2SiClN_3$ (?) for the first time.

A Nitrogen-free C_{21}-Steroid from Kurchi Bark

R. Tschesche, Ingrid Mörner, and *G. Snatzke*, Bonn (Germany)

Holadyson *(62)*, $C_{21}H_{28}O_4$, can be isolated from the neutral fraction of the extract from the bark of *Holarrhena antidysenterica* Wall. On the basis of its elemental composition and for biogenetic reasons it can be regarded as a steroid; this premise is supported by its mass spectrum. On account of its ultraviolet absorption (247.5 mμ), its infrared spectrum, and several color reactions, the presence of a $\Delta^{1,4}$-diene-3-one grouping is indicated; moreover, at least one hydroxyl group must be present. Its chemical properties indicate a cyclo-hemiacetal grouping. On hydrogenation with Adams' catalyst, four moles of hydrogen are taken up; subsequent oxidation gives a diketone $C_{21}H_{30}O_3$ *(63)* which no longer contains a hydroxyl group and readily gives a monoxime. The constitution of *(63)* appears from its NMR spectrum to be:



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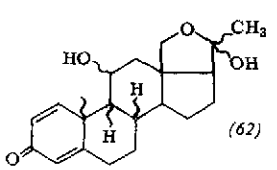


(62)

Holadysone *(62)* is therefore one of the possible stereoisomers of the (18→20)-hemiketal of $\Delta^{1,4}$-pregnadiene-11,18-diol-3,20-dione. The mass spectra of *(62)* and *(63)* give independent confirmation of the structures assumed. The positive circular dichroism of *(62)* differs from that of the usual $\Delta^{1,4}$-diene-3-one compounds, a fact which may be attributed to the influence of the cyclo-hemiacetal grouping and of an 11α-hydroxyl group or to anomalous stereochemistry at C-8, C-9, and/or C-10.

Composition and Linkage of the Sugars in the Saponins of Digitalis purpurea L.

R. Tschesche and *Günter Wulff*, Bonn (Germany)

Four cholesterol-precipitable saponins were isolated from the seeds of *Digitalis purpurea* L. In addition to the known saponins, digitonin and gitonin, two new compounds, deglucodigitonin and digalonin [35] were obtained. After methylation and hydrolysis, digitonin yielded 2,3,4,6-tetra-*O*-methyl-D-glucose, 2,3,4-tri-*O*-methyl-D-xylose, 2,3,6- and 2,4,6-tri-*O*-methyl-D-galactose, and 4,6-di-*O*-methyl-D-glucose. On partial acidic hydrolysis of the sugar chain, lycobiose, solabiose, and a small quantity of β-D-galactopyranosyl-(1→2)-D-glucopyranose were obtained. Degradation with HBr/glacial acetic acid gave both disaccharides and the oligosaccharides (isolated in crystalline form for the first time) digitotetrose and digitotriose B with the structures

gluc $\frac{1\rightarrow3}{\beta}$ gal $\frac{1\rightarrow2}{\beta}$ gluc $\frac{1\rightarrow4}{\beta}$ gal < and

gal $\frac{1\rightarrow2}{\beta}$ gluc $\frac{1\rightarrow4}{\beta}$ gal <, respectively.

It thus appears that digitonin has the structure 3-[β-D-glucopyranosyl(I)(1 → $3_{galact.II}$) - β - D - galactopyranosyl - (II)(1 → $2_{gluc.III}$)-β-D-xylopyranosyl(1 → $3_{gluc.III}$)-β-D-glucopyranosyl-(III)(1 → $4_{galact.IV}$)-β-D-galactopyranosyl(IV)(1→3β-digitog.)]-5α,20β$_F$,25α-spirostan-2α,3β,15β-triol [36].

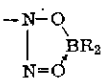
Digalonin contains the same sugars, while gitonin and deglucodigitonin each have one D-glucose unit less. The mother-liquor from the cholesterol precipitation contains further saponins which have the same genins, but apparently more sugars.

Reaction of Boron Compounds with Metal Chelates and Chelate-forming Compounds

F. Umland and *D. Thierig*, Hannover (Germany)

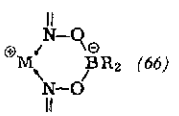
Boron compounds $M^{\oplus}[BR_4]^{\ominus}$, BR_3, and R_2BOH (R = aryl, alkyl, -O-aryl, -O-alkyl, halogen, or H) react with compounds which either possess or are capable of forming intramolecular hydrogen bonds. In the process, an R_2B-group replaces the proton of the hydrogen bridging bond; *e.g.* on reaction of diphenylborinic acid with $HF_2^{\ominus}$-ions, $[F_2BR_2]^{\ominus}$ is formed and can be precipitated as the ammonium salt from conc. NH_4HF_2 solution.

It proved possible to prepare carbon-free chelate rings of type *(65)*, *e.g.* with cupferron, and others with the BH_2-group, *e.g.* with 8-hydroxyquinoline.



(65)

Metal chelates with intramolecular hydrogen bonds such as bis(dimethylglyoximato)- [37] or bis(salicylaldoximato)-metal compounds form 6- or 5-membered metal chelate rings of type *(66)* and *(67)* which contain boron but are free from carbon.



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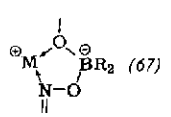


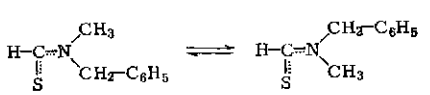
(67)

These compounds are extraordinarily stable, particularly if R = phenyl. They make it possible to carry out very sensitive, indirect estimations of traces of Cu, Ni, Co, Fe, and Pd, which can be determined quantitatively even in amounts of 10^{-9} g [38].

Studies on Thioformamides

W. Walter, Hamburg (Germany)

On treating chloroform with primary and secondary amines and NaSH, *N*-substituted thioformamides are obtained. *N*-Methyl-*N*-benzylthioformamide *(64)* occurs in two interconvertible modifications, one of which was prepared pure:



(64)

[34] See *W. Sundermeyer*, Chem. Ber. *96*, 1293 (1963).

[35] *R. Tschesche* and *G. Wulff*, Chem. Ber. *94*, 2019 (1961).

[36] *R. Tschesche* and *G. Wulff*, Tetrahedron, in the press.

[37] *F. Umland* and *D. Thierig*, Angew. Chem. *74*, 388 (1962); Angew. Chem. internat. Edit. *1*, 333 (1962); *G. N. Schrauzer*, Chem. Ber. *95*, 1438 (1962).

[38] *G. S. Spicer* and *I. D. H. Strickland*, Analytica chim. Acta *18*, 231 (1958).

Judging from infrared and NMR spectra, geometric isomerism is concluded to be involved. This is the first time that the *cis*- and *trans*-isomers of an open-chain thioamide have been separated.

New Reactions of Bis-(1,3-diphenyl-2-imidazolidinylidene)

H.-W. Wanzlick, H. Ahrens, B. König, and *M. Riccius*, Berlin (Germany)

The dimer of 1,3-diphenyl-2-imidazolidinylidene *(68)* serves as a carbene source [39]. Exchange reactions with compounds with acidic CH-groups leads to imidazolidine derivatives, some of which are of interest because of their preparative value (as potential aldehydes). Thus, for example, they afford a route to the hitherto unknown class of compounds, the β-sulfone aldehydes. The reactivity of the partners increases with increasing proton mobility. Acetic anhydride also reacts as a CH-acidic compound; hydrolysis of the primary product yields 1,3-diphenyl-2-methylimidazolidine and mono-acetylated dianilinoethane. On reaction with sulfur, the thiourea derivative of compound *(68)* is obtained, even at room temperature. Diazo compounds react with *(68)*, not with loss of nitrogen as in the case of dichlorocarbene [40], but to form ketazines. Acid chlorides give imidazolinium salts acylated at C-2 whose ready hydrolytic cleavage seems noteworthy with regard to the biochemical function of tetrahydrofolic acid [41].

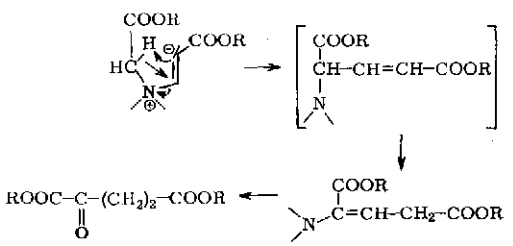
Reactions of Alkynylcarboxylic Esters with Tertiary Amines

E. Winterfeldt, Berlin (Germany)

The reaction between tertiary amines and propiolic (propargylic) ester normally proceeds very vigourously and with total resinification but leads to definite reaction products at high dilution and low temperatures. Although propiolic ester dimerizes in anhydrous medium to 1-butene-3-yne-1,4-dicarboxylic ester, in the presence of compounds containing active hydrogen addition to the triple bond occurs. One molecule of water adds on two molecules of propiolic ester to give the hitherto unrecorded compound di(-β-alkoxycarbonyl vinyl) ether *(69)*.

ROOC–CH=CH–O–CH=CH–COOR *(69)*

β-Aminocarbonyl compounds (ketones and esters) undergo Hofmann degradation under very mild conditions to yield β-aminoacrylic esters. α-Aminocarbonyl compounds are alkylated by Michael addition at the α-carbon atom; the enamines thus formed may be saponified to yield ketones.



The same reaction is also observed with vinylogous compounds of the γ-aminocrotonic ester type.

[39] Cf. *H.-W. Wanzlick*, Angew. Chem. *74*, 129 (1962); Angew. Chem. internat. Edit. *1*, 75 (1962).

[40] *H. Reimlinger*, Angew. Chem. *74*, 153 (1962); Angew. Chem. internat. Edit. *1*, 156 (1962).

[41] Cf. *L. Jaenicke*, Angew. Chem. *73*, 449 (1961).

Methods for the Determination and Separation of Gold

Max Ziegler, Göttingen (Germany)

Gold can be extracted as tributylammonium chloroaurate and separated electrolytically from a non-aqueous solution of this compound.

Amine *N*-oxides and substituted amides are suitable extracting agents for the separation of gold from 10^5-fold amounts of transition metals. Some dialkylformamides, dialkylacetamides, substituted ureas, and substituted amides of mineral acids are suitable for extracting small quantities of gold from large quantities of metals of the platinum group by means of liquid/liquid extraction. The degree of substitution and arrangement of the substituents in urea is important, *e.g.* hexamethylphosphoric acid tri-amide is very suitable.

Substituted acetylides of gold are readily extractable. Gold can also be separated from large excesses of other metals such as bis(trimethyl)hexamethylenediammonium tetrabromoaurate(III) and determined gravimetrically.

Hemiacetals and Acetals Containing Combined Hydroxylamines and Hydrazines

G. Zinner, Marburg/Lahn (Germany)

Distillable *O*- and *N*-hemiacetals derived from hydroxylamines: $R_2N–O–CHR'–OH$ and $RO–RN–CHR'–OH$, can be converted into a number of new types of acetals, *e.g.*

$R_2N–O–CH_2–NR_2$
$R_2N–O–CH_2–NR–NR_2$
$RO–RN–CH_2–NR_2$
$RO–RN–CH_2–NR–NR_2$
$RO–RN–CH_2–SR$ and
$RO–RN–CHR'–NR–OR$.

Full acetals derived from hydrazines and higher aldehydes ("hydrazinals") undergo a Mannich-type thermolysis reaction to give *N*-dialkylaminoalkyleneamines ("alkylene hydrazines") *(70)*.

$$R_2N–RN–CH(CH_2–R)NR–NR_2 \rightarrow \underset{(70)}{R_2N–RN–CH=CH–R} + R_2N–RNH$$

Hydrazinals from formaldehyde are cleaved by acyl chlorides to give stable, solid chloromethylhydrazines *(71)* (cf. the Böhme reaction).

$$R_2N–RN–CH_2–NR–NR_2 + \text{Acyl-Cl} \rightarrow \underset{(71)}{R_2N–RN–CH_2Cl} + \text{Acyl}–NR–NR_2$$

With alkanesulfinyl chlorides, only R–SO–S–R and R–S–S–R are formed; no sulfinylhydrazides, $R_2N–RN–SO–R$, have yet been isolated. With chlorosulfinic esters, however, smooth cleavage to $R_2N–RN–SO–OR$ occurs. In contrast, aminals and alkoxyaminals are degraded to $R_2N–SO–R$ and $RO–RN–SO–R$ on treatment with alkanesulfinyl chlorides. As expected, treatment of hydroxyaminals with chloro(thio)formic esters affords $HO–RN–C(O,S)–OR$, which can be converted into 3,5-diketo-1,2,4-oxadiazolidines by reaction with $C_6H_5N=C=O$ and cyclization [42].

Cleavage of *N,S*-acetals ($R_2N–RN–CH_2–SR$ and $RO–RN–CH_2–SR$) with chlorosulfinic esters gives thiosulfurous esters RS–SO–OR. [VB 704/98 IE]

German version: Angew. Chem. *75*, 673 (1963).

[42] *G. Zinner*, Arch. Pharmaz. *294*, 765 (1961).

Studies on the Active Centre of Ribonuclease

E. A. Barnard, London (England)

Virtually the only group in an enzyme active centre that can be fully identified and located, with reasonable confidence at present, is the histidine residue 119 in pancreatic ribonuclease. It is difficult to prove that a group is a direct participant in an active centre and is not only essential owing to some other, protein structural, role. Direct participation appears here to be substantiated by the convergence of evidence:

(1) Reaction of the enzyme with bromoacetic acid gives specific, complete inactivation when one carboxymethyl group is introduced [1]; this group is uniquely located at histidine residue 119 [2].

(2) We have obtained the pure derivative by ion-exchange chromatography; it closely resembles native ribonuclease in physical properties, *e.g.* sedimentation constant (S_{20}), spectrum, etc.

(3) The reaction of bromoacetate with the enzyme is much faster than that with free histidine, and shows an anomalous dependence on pH (optimum pH 5.5).

(4) Reaction with iodoacetate [3] proceeds similarly; iodoacetamide does not react [4].

(5) The reaction requires the native enzyme; oxidized or reduced ribonuclease does not react. It can occur to some extent in urea [5] but not in all preparations [4]; this point requires further investigation.

(6) Cytidine-2′- or -3′-phosphates are strong competitive inhibitors for ribonuclease and greatly protect it from attack by bromoacetate.

(7) Photoxidation independently shows that a histidine is essential for the enzymatic activity [6].

The dependence on pH of ribonuclease kinetics [7, 8], as well as of the halogenoacetate reaction, suggests that two histidine residues are involved. That the second basic group is not an $-NH_2$ of low pK is shown by reaction of guanidinated [9] ribonuclease with bromoacetate, when the reaction proceeds with the same pH profile as that obtained with native ribonuclease. Recently, direct evidence for participation of histidine residue 12 has been reported [10].

119-Carboxymethyl-ribonuclease has lost almost all binding affinity for cytidine-2′-phosphate, as was confirmed by a direct ultracentrifugal method [11], suggesting histidine residue 119 is at the substrate binding site. The kinetics of each of the two steps of the enzyme-substrate reaction have been determined on a series of substrates and support the involvement of two histidines in binding the substrate.

Bromoacetic acid is thus the simplest case of a substrate-like reagent, being bound as is the $P-O^{\ominus}$ of the substrates, to alkylate a nucleophilic component at the binding site. In contrast to the behavior of ribonuclease, we find no comparable inactivation of lysozyme by bromoacetic acid (0.18 M, pH 4 to 8.5). Lysozyme probably involves a histidine residue in its active centre [12], but has uncharged substrates.

Other groups must also be concerned in the active centre of ribonuclease. Recent studies [13] show the acylation of a specific lysine residue, and allow its relationship to the imidazole system to be explored.

[Lecture to the Basler Chemische Gesellschaft, Basel (Switzerland), April 25th, 1963] [VB 713/95 IE]

German version: Angew. Chem. *75*, 734 (1963).

[1] *E. A. Barnard* and *W. D. Stein*, J. molec. Biol. *1*, 339 (1959).

[2] *W. D. Stein* and *E. A. Barnard*, J. molec. Biol. *1*, 350 (1959).

[3] *H. G. Gundlach, W. H. Stein*, and *S. Moore*, J. biol. Chemistry *234*, 1754 (1959).

[4] *G. R. Stark, W. H. Stein*, and *S. Moore*, J. biol. Chemistry *236*, 436 (1961).

[5] *E. A. Barnard* and *W. D. Stein*, Biochim. biophysica Acta *37*, 371 (1960).

[6] *L. Weil* and *T. S. Seibles*, Arch. Biochem. Biophysics *54*, 368 (1955).

[7] *D. G. Herries, A. P. Mathias*, and *B. R. Rabin*, Biochem. J. *85*, 127 (1962).

[8] *H. Witzel* and *E. A. Barnard*, Biochem. biophys. Res. Commun. *7*, 289, 295 (1962).

[9] *W. A. Klee* and *F. M. Richards*, J. biol. Chemistry *229*, 489 (1957).

[10] *A. M. Crestfield*, Fed. Proc. *22*, 419 (1963).

[11] *E. A. Barnard* and *A. Ramel*, Nature (London) *195*, 243 (1962).

[12] *H. Fraenkel-Conrat*, Arch. Biochem. Biophysics *27*, 109 (1950).

[13] *E. A. Barnard* and *S. Shall*, unpublished results.

Flash Photolysis and Fluorescence of Ammonia

W. Groth, Bonn (Germany)

A new flash arrangement for use in the vacuum ultraviolet down to 1150 Å and based on the work of *Bayes*, *Becker*, *Stuhl*, and *Welge* was described. The reaction and discharge chambers are separated by a series of LiF windows. The total energy of 1870 watt-sec is distributed over 12 parallel spark gaps, which are flashed synchronously. The resolution time can thus be decreased to $\leq$ 2 μsec. (A similar flash arrangement for the quartz ultraviolet range with 5 parallel spark gaps has a resolution time of 3.7 μsec. with a total energy of 1440 watt-sec.).

During flash photolysis of ammonia, the NH radical was detected in addition to the NH_2 radical, at wave lengths of $<$ 1550 Å [(0,0)-and (1,1)-bands of the transition $^3\Pi \rightarrow {}^3\Sigma^-$]. The dependence of the NH concentration on the delay time of the analysis flash, on the NH_3 pressure, and on the nature of diluent gases was examined. The NH radical arises with certainty as primary product of the photolysis by the reaction $NH_3 + h\nu \rightarrow NH + H_2$ or $NH + 2\,H$.

During fluorescence analysis using the resonance wave lengths of krypton (1165 Å, 1235 Å) and xenon (1295 Å, 1470 Å) only the (0,0) bands of the $^1\Pi \rightarrow {}^1\Delta$ transition were detected, but not the $^3\Pi \rightarrow {}^3\Sigma^-$ transition proposed by *Neuimin* and *Terenin*. There are two possible modes of formation of the NH radicals in the $^3\Sigma^-$ ground state that were detected by flash photolysis: 1. direct transition into this state; 2. transition to a singlet, with subsequent radiationless transition to the $^3\Sigma^-$ ground state. For a decision, experiments with greater sensitivity of the equipment would be required. Upper limits of the collision yields of reactions of the NH radicals can be estimated.

During photolysis of NH_3 with krypton and xenon lines, the relative yield of hydrazine is the same in experiments, with high gas flow rates, as those obtained with the Hg-line at 1849 Å; the NH radicals must therefore react with NH_3 to give N_2H_4. The quantum yield of the NH_3 decomposition with the short wavelengths is greater by a factor of 1.3 to 1.6 than that at 1849 Å. H_2 in large excess has no influence on the quantum yield. On addition of CO, only formamide could be detected as a further reaction product.

[GDCh-Ortsverband Mainz-Wiesbaden (Germany), May 2nd, 1963] [VB 709/92 IE]

German version: Angew. Chem. *75*, 734 (1963)

Oxidative Hydrolysis of Phosphorus Sulfides

H. Falius, Braunschweig (Germany)

The work of *Treadwell* and *Beeli* [1] and of *Pernert* and *Brown* [2] on the hydrolysis of phosphorus sulfides throws no light on the constitution of the sulfides, owing to the occurrence of redox and isomerization reactions. In the

[1] *W. D. Treadwell* and *C. Beeli*, Helv. chim. Acta *18*, 1161 (1935).

[2] *J. C. Pernert* and *J. H. Brown*, Chem. Engng. News *27*, 2143 (1949).

presence of oxidizing agents, these reactions are retarded and the P–P bonds in the sulfides, whose presence was demonstrated some years ago by X-ray structural analysis, remain unaltered. Since the P–P bonds in phosphorus oxyacids are stable in alkaline solution and in order to avoid the presence of foreign ions, the lower phosphorus sulfides P_4S_3, P_4S_5, and P_4S_7 were hydrolysed in solutions of various alkalinities with hydrogen peroxide as oxidizing agent. The following oxyacids of phosphorus were obtained (the percentage yields are based on the initial quantity of phosphorus and are approximately average values for all the hydrolyses):

P_4S_7: 10 % phosphite, 55 % phosphate, 5 % pyrophosphate, 25 % hypophosphate, 5 % triphosphate (V, IV, IV).

P_4S_5: 10 % phosphite, 40 % phosphate, 10 % pyrophosphate, 25 % hypophosphate, 10 % triphosphate (V, IV, IV), 5 % triphosphate (IV, III, IV).

P_4S_3: 10 % phosphite, 35 % phosphate, 5 % pyrophosphate, 20 % hypophosphate, 15 % triphosphate (V, IV, IV), 15 % triphosphate (IV, III, IV).

The qualitative and quantitative analyses were carried out using paper chromatography with photometric measurements. The stability of phosphite and hypophosphate in the reaction solution was tested and confirmed. Pyrophosphate and triphosphate (V, IV, IV) must have been formed by a reaction mechanism similar to that of the oxidative hydrolysis of thiophosphates to form pyrophosphates. This was investigated in more detail. Starting from monothiophosphate 0 %, from dithiophosphate 16 %, and from tetrathiophosphate 12 % pyrophosphate (yield based on phosphorus) was formed.

[GDCh-Ortsverband Braunschweig (Germany), May 13th, 1963] [VB 708/89 1E]

German version: Angew. Chem. 75, 735 (1963).

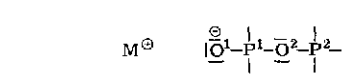
Structural Chemistry of Crystalline Phosphates

F. Liebau, Würzburg (Germany)

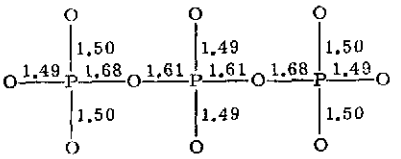
Considerations of the structures of inorganic phosphates can begin either from $[PO_4]$ tetrahedra or from the coordination polyhedra of the cations which can gradually be built up into larger and larger units. In the former case, for example, one proceeds from the discrete tetrahedra of monophosphates via the double and triple tetrahedra of the di- and triphosphates to the ring and chain form anions of meta- and polyphosphates. The possibility of linking $[PO_4]$ tetrahedra to form layer and framework structures was also demonstrated. It is not surprising that several phosphate structures are isotypic with silicates.

In starting structural considerations from cation polyhedra, one proceeds in a similar way, for example, from structures with discrete $[M(O,OH)_6]$ octahedra to double and triple octahedra and octahedron chains and layers. However, whereas the $[PO_4]$ tetrahedra condense to share common apexes, the cation polyhedra can also unite to share common edges and faces.

The P–O bond in phosphates has some polar and some covalent character. The four σ-bonds, due to sp^3 hybridization are the most favorable energetically and give rise to the tetrahedral arrangement of the oxygen atoms around the



phosphorus atom. The free electron pairs of the oxygen atoms are partially drawn into the d_{z^2} and the $d_{x^2-y^2}$ orbital of the phosphorus to form two π-bond systems, which in condensed phosphates are involved in the whole -O-P-O-P-O- chain. Since the cations (M) are less electronegative than the phosphorus, the former act as electron donors and "push" electrons from oxygen atom O-1 into the π-bond over towards the phosphorus atom P-1. Hence the P(1)–O(1) bond is more strongly covalent and shortened. The P-1 atom attempts to pass on part of the electron charge to the oxygen bridge atom O-2 so as to enhance the polar character of the P(1)-O(2) bond, which as a consequence is lengthened. The effect of the cations should be such that a slight shortening of the O(2)-P(2) bond is noticeable. This is shown especially clearly in the interatomic distances of sodium triphosphate $Na_5P_3O_{10}$ (given in Å).



This effect of the cations in poly- and metaphosphates causes the distance between the phosphorus atom and the oxygen bridge atom to be about 1.62 Å, while the remaining P-O distances, with an average of 1.49 Å, are noticeably shorter. In accordance with the character of the P-O bond, the P-O-P valence angle in the structures investigated so far deviates only slightly from the mean value of 129°. The results of crystallographic investigations are thus in harmony with the theory of the chemical bond.

[Inorganic Chemistry Colloquium at the Universität Göttingen (Germany), May 20th, 1963] [VB 714/90 1E]

German version: Angew. Chem. 75, 735 (1963).

Recent Results in the Field of Homogeneous Catalysis of Gas Reactions

Z. G. Szabo, Szeged (Hungary)

The lecturer showed, by means of his latest experimental data, in particular by kinetic analysis of the thermal decomposition of propanal and acetaldehyde, that the theory on the influencing of homogeneous chain reactions developed by him and his co-workers can be confirmed exactly. Results of experiments performed under conditions of utmost cleanliness in the presence and absence of nitric oxide were entirely in conformity with the theoretical influencing factor and the order of reaction was determined at 3/2 without deviation. The values found for the thermodynamic variables were entirely plausible. The agreement of theory and practice shows that the influencing can be explained by assuming radical stabilization, which is reversible and which has an enthalpy of reaction of 15 kcal/mole. The theory permits description of the mechanism of catalysis and inhibition of homogeneous chain reactions from a unified standpoint and it offers the possibility of investigating radical properties, which would not be accessible to other methods. The relation of the views developed by the lecturer to the theories of other kinetic schools, such as those of *Hinshelwood* or of *Eyring* were discussed.

[GDCh-Ortsverband Ruhr, Mülheim/Ruhr (Germany), May 29th, 1963] [VB 710/93 1E]

German version: Angew. Chem. 75, 798 (1963).

The Structure of the Intermediate in Electrophilic Aromatic Substitutions

H. Zollinger, Zürich (Switzerland)

By suitable choice of reactants in electrophilic substitutions, the relative velocities of the steps of electrophilic substitutions can be varied widely. In suitable cases, the structure of the intermediate in this type of substitution can thereby be ascertained. Investigations of the nuclear magnetic resonance of the intermediates obtained in the bromination and iodi-

nation of 2-naphthol-6,8-disulfonic acid [1] can be extended to other reactions. Thus it was found, surprisingly, that the intermediate in the iodination of 4,4'-bis(dimethylamino)-diphenylethylene is not a σ-, but a π-complex. The originally surprising observation that the nuclear magnetic resonance spectra of π-complexes are almost identical with those of the starting materials can be explained by superposition of two effects which occur on complex formation and which influence the position of the nuclear magnetic resonance signal, *viz.* the change in the electron density of the electron donor and the change in the aromatic ring current. From the magnitude of kinetic hydrogen-isotope-effects on electrophilic substitution reactions, conclusions can be drawn regarding the structure of the initial state of the proton-transfer stage.

[GDCh-Ortsverband Göttingen (Germany), May 30th, 1963] [VB 724/96 IE]

German version: Angew. Chem. *75*, 799 (1963).

Radical Addition Reactions of Allenes

T. L. Jacobs, Los Angeles, Calif. (U.S.A.)

Ethyl- and phenylthiyl radicals add onto allene, 1,2-butadiene, and 3-methyl-1,2-butadiene to give 1:1 and 2:1 adducts in high yield. Ethyl thiol and allene yield a mixture of ethyl allyl sulfide, 1,2-di(ethylthio)propane, and 1,3-di-(ethylthio)propane at 70 °C with azo-bis-isobutyronitrile initiator. Thus, 13 % attack occurs at the center carbon and 87 % at the terminal carbons. The reaction is inhibited by 4-t-butylpyrocatechol.

Attack of ethylthiyl radicals on 1,2-butadiene occurs at all three positions to give a mixture of *cis*- and *trans*- crotyl ethyl sulfide, ethyl 2-methylallyl sulfide, *cis*- and *trans*-2-ethylthio-2-butene, and *meso*- and (±)-2,3-bis(ethylthio)-butane. The products were separated and determined by vapor phase chromatography. The method does not exclude the possibility that small amounts of 1,2- and 1,3-di(ethylthio)butanes were also present. It was shown by separate experiments that ethyl crotyl sulfide rearranges slightly to ethyl α-methylallyl sulfide under the experimental conditions and that the latter gives considerable rearrangement to the former; thus, the percentages of addition to carbon atoms 1 and 3 are uncertain, although some attack at C-3 seems certain. Attack at the center carbon occurs to the extent of 48 %; the products indicate 46 % attack on C-1 and 6 % on C-3.

Both ethyl- and phenylthiyl radicals attack 3-methyl-1,2-butadiene at the center carbon of the allenyl system. Additions of ethylthiyl radicals onto propyne, 1- and 2-butyne, and 1,3-butadiene were studied because these compounds are possible rearrangement products of the allenes. It was shown that additions onto the allenes are not accompanied by rearrangement to these hydrocarbons and that the allene additions do not occur by prior rearrangement and rapid addition to rearrangement products.

[GDCh-Ortsverband Würzburg (Germany) May 31st, 1963] [VB 721/88 IE]

German version: Angew. Chem. *75*, 798 (1963).

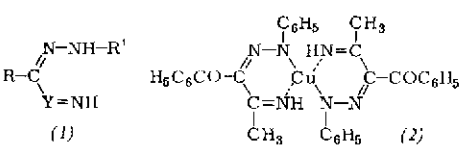
[1] *M. Christen, W. Koch, W. Simon*, and *H. Zollinger*, Helv. chim. Acta *45*, 2077 (1962).

SELECTED ABSTRACTS

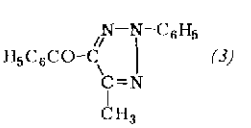
Coleone A and B, two new leaf pigments, have been isolated and characterized by *C. H. Eugster, H.-P. Kung, H. Kuhnis*, and *P. Karrer*. Dried leaves of the African shrub *Coleus igniarius* (Schweinf.) were extracted with benzene, partitioned between petroleum ether/benzene/methanol/water and chromatographed on polyamide (Glilon® powder). Coleone A *(1)*, $C_{20}H_{22}O_6$, formed bright-red prisms, m.p. 136–136.5 °C, $[\alpha]_D^{23} = +100°$ (alc.), +80° (chlf.); is reduceable with dithionite, Zn, or sulfite to the leuco compound, is reoxidizable with air, forms heavy metal complexes and a violet-red boric acid complex, is soluble in NaOH and soda solutions, and forms a monomethoxy compound. Coleone B *(2)*, $C_{19}H_{20}O_6$, yields ochre-yellow to light-orange prisms, m.p. 258–259 °C, $[\alpha]_D \approx +130°$ (alc.), −16° (chlf.), is not reduceable, forms a yellow triacetate of m.p. 174–176 °C, a trimethyl ether (yellow needles, m.p. 107–108 °C), a tetramethyl ether (m.p. 120–121 °C) and differs markedly from *(1)*. Compound *(1)* is a quinone related to droserone; *(2)* does not appear to be a quinone. / Helv. chim. Acta *46*, 530 (1963) / −De. [Rd 582/164 IE]

Physiological side effects of phenolphthalein. Administration of large amounts of phenolphthalein as a laxative can give rise to abdominal colic, palpitations, and occasionally collapse. Skin rashes have frequently been reported; at times these are distributed over the whole body and not infrequently produce ulceration or blistering as well as pigment reactions. An allergic reaction to phenolphthalein has recently been observed by *K. J. B. Lewin*. This manifested itself as a recurrent illness with fever, rash, pains in the knee joints, and pericarditis; these symptoms simulate those of Lupus erythematodes disseminatus (tuberculous erysipelas), a recurrent and invariably fatal disease. The patients had used the laxative for several years before the first allergic reaction appeared. It is remarkable that the allergic reactions disappeared for a year after the appearance of the first symptoms, although the laxative was still taken during this period. / Arch. Toxikol. *20*, 28 (1963) / −R. [Rd 585/165 IE]

The synthesis of vicinal triazoles has been described by *B. Hirsch* and *J. Ciupe*. Arylhydrazones of 1,2-disubstituted glyoxalimines of type *(1)*, where *e.g.* R = H_5C_6CO, R' = H_5C_6, and Y = $H_3COC_6H_4$, react in alcohol with an ammoniacal Cu(II)-salt solution to give the Cu-complex *(2)*, which can be isolated. On heating the solution, the complex decomposes with



(1) *(2)*



(3)

formation of the triazole derivative *(3)*. In general, compounds *(1)* with Y = C(alkyl), or C(aryl) and R and R' as above may be converted into triazoles in good yield by short heating with an ammoniacal solution of a copper salt. / Chimia *17*, 159 (1963) / −Ma. [Rd 620/178 IE]

Fabianite, $CaB_3O_5(OH)$, a new mineral, was discovered by *H. Gaertner, K.-L. Roese*, and *R. Kühn* in deformed permian limestone 1 (natural gas well at Rehden near Diepholz, Germany). The well-formed idiomorphic crystals, 0.3–2.5 cm in size, had the following properties: crystal face planes (100), (110), (011), (021); monoclinic prismatic; axial ratio 0.7960: 1:0.6261, β = 113°10'; $n_\beta \| h$, $n_\gamma \| a$, $n_\alpha \sphericalangle C$ 23.3°; 2 V_α = 64.7°; optically negative, $n_\alpha = 1.608_5$, $n_\beta = 1.637_5$, $n_\gamma = 1.650_0$ (Na light); H = 6; D = 2.796. The crystals are very probably secondary formations. / Naturwissenschaften *49*, 230 (1963) / −Ma. [Rd 619/177 IE]

Very pure trialkylindium compounds were prepared by *E. Todt* and *R. Dötzer*. They fused technical In (containing up to 5 % impurities) with technical Mg in an atmosphere of hydrogen. Fine turnings of this alloy (or mixtures of In and Mg) were covered with ether and treated with alkyl halides under a blanket of specially purified nitrogen or argon.

After the reaction, the trialkylindium compounds can be distilled off as etherates; a second distillation is usually sufficient to remove the ether. The etherate of trimethylindium can be decomposed by distillation with a little benzene. Trimethylindium *(1)* forms colorless crystals (b.p. 66 67 °C/12 mm; m.p. 88.4 °C) and is completely stable to light and heat, even at 250 °C. The triethyl, tri-n-propyl, tri-isopropyl *(2)*, tri-n-butyl, tri-isobutyl, and tri-s-butyl *(3)* derivatives of In are faintly viscous, colorless liquids; *(2)* and *(3)* are yellow. All these compounds ignite spontaneously in air and react violently with water. With the exception of *(1)*, they are decomposed by light and by heating to 200 °C, or less, the metal being deposited. Indium purified in this manner is suitable for the preparation of $A^{III}\,B^{V}$ compounds for semi-conductors. / Z. anorg. allg. Chem. *321*, 120, (1963) / Kr.

[Rd 608/170 IE]

BOOK REVIEWS

German-English Chemical Terminology. An Introduction to Chemistry in English and German, by *H. Fromherz* and *A. King*. Verlag Chemie GmbH., Weinheim/Bergstr. 1963. 4th Edit., XXI, 588 pp., linen, DM 48.– (about $12.–).

The ability to read chemical literature in a foreign language is now a necessity for students. Any knowledge of languages brought from school, however, has not normally been acquired from scientific texts, and the specialised modes of expression of the latter are therefore often found very difficult to understand. Here the "Introduction to Chemistry in English and German" offers valuable help. The basic idea of the book is as simple as it is fortunate. German and English texts are printed facing one another on adjacent pages, each technical term is in italics, and page subdivision in the margin facilitates orientation. The whole is a condensed textbook of chemistry and its related subjects, concluding with a list of abbreviations, a subject index in English, a guide to the pronunciation of English technical terms, and a subject index in German. The agreement between the German and English phraseology in the text is good – except for a few mistakes –, and as close as the style of each language permits. In the choice of material and in its clear and compact presentation, the authors have found just as fortunate a touch as in their translations of relevant sections into the other language. Any chapter of the text may be selected and read on its own and thus a feeling gained for modes of expression in English and German scientific works. The book can also be used just as well as a two-language dictionary – it has over 10000 terminological entries. It is this twofold function which makes the volume so especially useful for students, scientists, and translators.

H. Grünewald [NB 26/52 IE]

Progress in Drug Research – Fortschritte der Arzneimittelforschung – Progrès de recherches pharmaceutiques, edit. by *E. Jucker*, Vol. IV, Birkhäuser, Basel-Stuttgart 1962. 1st Edit., 606 pp., bound, DM 118.– (about $30.–).

The fourth volume of the series begun in 1949 [1] again presents detailed reviews by expert authorities on current problems in drug research. In the first 212 pages *H. Herbst* describes "New Developments in the Field of Therapeutic Organic Sulfur Compounds." The first section of the article is devoted to sulfur-containing drugs and antibiotics, while in the second, organotrophically active organic sulfur compounds are dealt with. Besides the chemistry of the compounds, the methods of synthesis of the most important representatives are given, and the mechanism of action, fate in the organism, and methods of detection are briefly mentioned; 1958 references to patents and journals give access to the original articles.

N. J. Harper then describes "Drug Latentiation" in 74 pages. This new term is used to describe the chemical modification (in the laboratory) of a biologically active compound into an inactive form which is transformed *in vivo* into the active substance. The term also covers modifications simply of physico-chemical properties that cause changes in resorption, distribution, and metabolism of the compound in question without influencing its activity. These transformations are illustrated by numerous examples and can also stimulate improvements of existing preparations with regard to resorption, compatibility, *etc.* (359 literature references).

In the next chapter (54 pages), *E. Schlittler*, *J. Druey*, and *A. Marxer* report on "Antihypertensive Agents." It is subdivided into sympatholytics, parasympatholytics, ganglion blocking agents, hydrazinophthalazines, *Rauwolfia* alkaloids, *Veratrum* alkaloids, guanidines and amidoximes, saluretics, and other compounds. By giving numerous examples the connection between constitution and activity is also suggested (191 literature references). The "Connection between Constitution and Activity in Local Anaesthetics" is treated in 47 pages by *H. Grasshof*. Starting out from the basic structure, lipophilic residue – intermediate chains with an electronegative link – hydrophilic residue, the influence of each of these parts on the activity is described. Numerous examples in 29 tables are an aid to easy understanding (121 references).

The last chapter by *J. C. Arcos* and *M. Arcos* deals with the problem of "Molecular Geometry and Mechanisms of Action of Chemical Carcinogens" (174 pages). The major portion is devoted to the relationship between structural parameters and carcinogenic activity in the various groups of carcinogenic compounds. Further sections deal with the possible types of combination of carcinogens with tissue constituents and finally with submicroscopic cell structures (876 literature references).

The layout of the book is exemplary; numerous structural formulae make the reading of it much easier. An especially welcome feature is its 22-page comprehensive subject index covering all the reports.

O. Schaumann [NB 19/48 IE]

[1] Vols. II and III, cf. Angew. Chem. internat. Edit. *1*, 607 (1962).

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1,3-Dipolar Cycloadditions
Past and Future [*]

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In contrast to the very large number of special methods applicable to syntheses in the heterocyclic series, relatively few general methods are available. The 1,3-dipolar addition offers a remarkably wide range of utility in the synthesis of five-membered heterocycles. Here the "1,3-dipole", which can only be represented by zwitterionic octet resonance structures, combines in a cycloaddition with a multiple bond system – the "dipolarophile" – to form an uncharged five-membered ring. Although numerous individual examples of this reaction were known, some even back in the nineteenth century, fruitful development of this synthetic principle has been achieved only in recent years.

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A study of the mechanism of addition of diazoalkanes to angularly strained double bonds which was conducted in 1957–58 in our Munich laboratory led to the concept of 1,3-dipolar cycloaddition. 1,3-Additions of diazoalkanes, azides, and ozone, which conform to this scheme, have been known for over 50 years. *L. I. Smith* [1] published a comprehensive review of open-chain and cyclic 1,3-additions of this type, without, however, considering possible extensions of the reaction. It was only after the reaction scheme was generalized [2] that the prediction and discovery of new classes of 1,3-dipoles and of numerous new reactions were achieved. The vigorous current development of this branch of chemistry makes it desirable to review the old and newly discovered 1,3-dipolar cycloadditions. A second paper, to appear shortly in this journal, will deal with the kinetics and mechanism of 1,3-dipolar cycloadditions.

[*] Extended version of lectures given at the Chemists' Meeting in Vienna (Austria) October 1961, and at the Gordon Research Conference, New Hampton (U.S.A.), 1961.

[1] *L. I. Smith*, Chem. Reviews *23*, 193 (1938).

[2] *R. Huisgen:* Festschrift zur Zehnjahresfeier des Fonds der Chemischen Industrie, Düsseldorf 1960, p. 73; Proc. chem. Soc. (London) *1961*, 357; Chem. Weekblad (Amsterdam) *59*, 89 (1963).

A. Definition and Classification

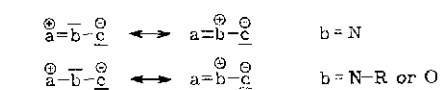
1. Description and Classification of 1,3-Dipoles

Cycloadditions can be classified according to the number of new σ-bonds formed or according to the size of the ring which is formed. In the most frequent case, two reactants unite to form the cyclic compound, creating two new σ-bonds at the expense of two π-bonds [3]. The thermal or photochemical formation of cyclobutanes from alkenes and the Diels-Alder synthesis are two important cycloadditions in which 4- and 6-membered rings, respectively, are produced.

A cycloaddition of the type 3 + 2 → 5 leading to an uncharged 5-membered ring cannot possibly occur with octet-stabilized reactants which have no formal charges. Rather, a 1,3-dipole, *a-b-c*, must be defined, such that atom *a* possesses an electron sextet, *i.e.* an incomplete valence shell combined with a positive formal charge, and that atom *c*, the negatively charged center, has an unshared electron pair. Combination of such a 1,3-dipole with a multiple bond system *d-e*, termed the dipolarophile, is referred to as a 1,3-dipolar cycloaddition. The two components coalesce by means of a cyclic electron displacement with extinction of the formal charges to give a 5-membered ring. The dipolarophile may be any double or triple bond.

As with other nomenclature proposals, the term "1,3-dipolar addition" does not exclude the possibility of misunderstandings. The term is derived from the fact that compounds which can only be represented by zwitterionic all-octet resonance structures are ambivalent in the 1- and 3-positions, thus displaying electrophilic as well as nucleophilic activity. The dipolarophile can be any double or triple bond.

Compounds containing an electron sextet at a carbon, nitrogen, or oxygen atom are not stable. The foregoing designation would therefore acquire the physical significance of a mere resonance contributor if the 1,3-dipole were capable of isolation. Stabilization is possible if an unshared pair of electrons at atom *b* can relieve the electron deficiency at center *a* by formation of an additional bond. In the new mesomeric formula, in which *b* now has the positive charge, all the centers have completely filled valence shells. Such systems will be designated as 1,3-dipoles with internal octet stabilization.



Sextet formula Octet formula

The sextet structure of the 1,3-dipoles may contain either a double or a single bond between *a* and *b*. When a double bond is present and we confine ourselves to the lowest group of eight elements in the periodic table, then the middle atom, *b*, whose free electron pair is borrowed by the sextet center, *a*, must be nitrogen. No other element has an extra pair of electrons available while remaining in the triply bonded neutral state. In the 1,3-dipoles where no double bond is present in the "unmasked" (sextet) formula, the role of the center *b* can be assumed by either a nitrogen function or an oxygen atom.

A simple classification system for 1,3-dipoles is obtained when C, N, and O atoms, in that order, are successively made to carry the positive and the negative charges of the sextet formula. With the centers *a-b-c* limited to these three elements, six "1,3-dipoles with double bonds" can be visualized. All of these contain nitrogen as the middle atom and all belong to either the nitrilium or the diazonium betaines. Thus, the left-hand side of Table 1 shows the sextet structure with an electron deficiency at *a* and a free electron pair at *c*; this formula is the obvious symbol for the 1,3-reaction path. The right-hand side of the table gives the all-octet formula which reveals the relationship between these 1,3-dipoles and the nitriles or the nitrogen molecule. In this classification, the carrier of the anionic charge within each group is successively the carbanion, the imide nitrogen, and the oxide oxygen.

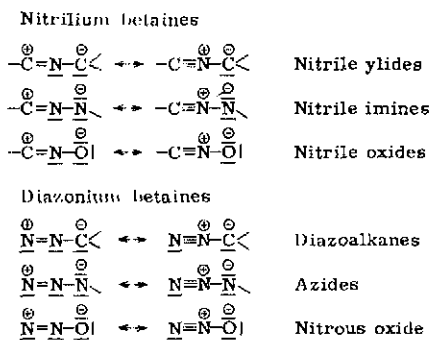
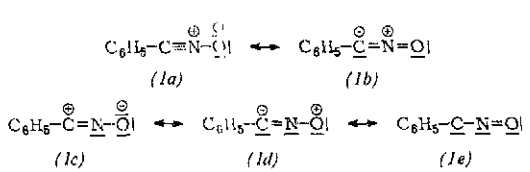


Table 1. 1,3-Dipoles with a double bond and internal octet stabilization

An oxygen sextet with a positive formal charge cannot participate simultaneously in a double bond. Hence, an oxygen atom cannot assume the position of the sextet center *a*. However, one can conceive of oxenium formulae in which there is a double bond between *b* and *c*. These are not derived from new 1,3-dipoles, but are simply further mesomeric structures of systems already considered in Table 1. Thus, for example, two octet formulae can be written for benzonitrile oxide, *viz. (1a)* and *(1b)*, which define the electron distribution in the ground state and show that the negative charge distributes itself between the carbon and oxygen atoms, resulting in considerable net charge cancellation. It is therefore misleading to assume that 1,3-dipoles must have a high electric moment in the ground state. Of the three possible sextet structures of benzonitrile oxide, *(1c)* and *(1d)* indicate the possibility of charge exchange,

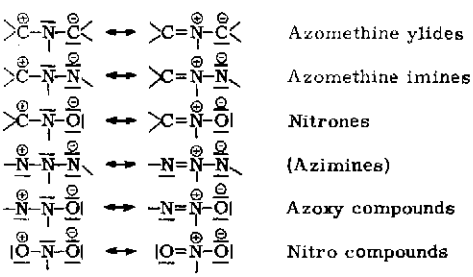


[3] Cf. *R. Huisgen, R. Grashey,* and *J. Sauer* in *S. Patai:* Alkenes. Interscience, New York, in the press.

which is characteristic of all 1,3-dipoles given in Tables 1 and 2. Formula *(1e)* is devoid of charge and displays the character of a carbene (or of an azene for the corresponding diazonium betaine structures).

The resonance formulae with electron sextets no doubt make only a small contribution to the ground state, but they are capable of directing the course of reaction. This is not a novel idea; consider, for example, the benzenediazonium ion, whose octet formula with a triple bond between the two nitrogen atoms conceals the electrophilic character of the outer nitrogen. A minor resonance structure with an electron sextet at this nitrogen atom accounts for the reactivity of this ion toward phenoxide, cyanide, or sulfite anions. On the other hand, the sextet structures used in the following discussion should not be misconstrued as denoting "reaction formulae", *i.e.* no shift in the electron distribution to form the sextet formula must precede the 1,3-addition.

1. Nitrogen as central atom



2. Oxygen as central atom

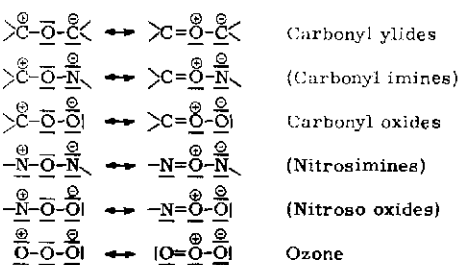
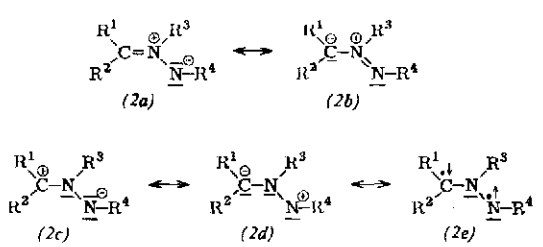


Table 2. 1,3-Dipoles without a double bond but with internal octet stabilization

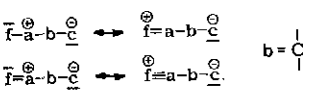
In Table 2 are presented structures which contain no double bond when written as the 1.3-dipole, *i.e.* the sextet formula. The greater variety of these dipoles is due to the fact that in this case either nitrogen or oxygen may occupy center *b*. Here, too, the charges are interchangeable. Thus, for example, Subclass 1 does not show "azylides" corresponding to the azoxy compounds. However, this absence is only superficial as the azylides are actually identical with the azomethine imines *(2)*, as shown by the mesomeric formulae *(2b)* and *(2d)*. Since nitrogen bears an anionic charge more readily than carbon, the arrangement rule given above automatically leads to the presentation of the more significant charge distributions in the Table.



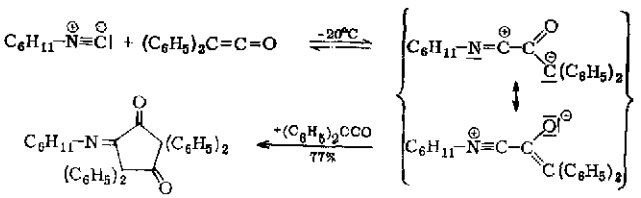
Here again, the two octet formulae of the azomethine imine are followed by structures with incomplete valence shells. One difference between this set of formulae and that of the 1,3-dipoles of Table 1 is the absence in this case of an uncharged sextet formula. Finally, the compound can also be written as a biradical *(2e)* which contains two electron septets and two single electrons with coupled spins.

With the exception of the four 1,3-dipoles shown in brackets in Table 2, which are still unknown, all the systems in Tables 1 and 2 have been employed in cycloadditions. Several of these 1,3-dipoles were unknown at the start of the investigations in our laboratory; others were applied for the first time in 1,3-dipolar cycloadditions.

If the center *b* of the 1,3-dipole *a-b-c* is a carbon function, then the internal octet stabilization is prevented by lack of an available free electron pair. However, it is possible for a ligand *f* on the sextet center *a* to possess an unshared electron pair and thus to provide external octet stabilization.



The number of cycloadditions carried out with this type of 1,3-dipoles is still so modest that any attempt at their classification appears at present to be unjustified. The reaction of isonitriles with ketenes may be mentioned as an example; the 1:2 adducts obtained are presumably 1-imino-2,4-cyclopentanediones [4]. A plausible intermediate, *viz.* a 1:1 adduct which may be formed reversibly, can be recognized as an externally stabilized 1,3-dipole, which subsequently combines with a second molecule of the ketene as the dipolarophile.



Neither the 1,3-dipole formed from the isonitrile and the ketene nor many of the other octet-stabilized 1,3-dipoles are stable enough to be isolated. Such systems must therefore be treated with the dipolarophiles *in situ*. If isolation of the 1,3-dipole is relinquished and extremely short-lived intermediates are trapped by reaction with the dipolarophilic reactant, then the restriction of octet stabilization of the 1,3-dipole can be overcome. Examples of this are given by the unsaturated carbenes and azenes of Table 3 [5]; here each mesomeric formula bears the blemish of an electron sextet. We selected the ketocarbenes from this class of compounds, and subjected them to 1,3-cycloadditions. The distribution of the positive and negative centers in these systems is

[4] *I. Ugi* and *K. Rosendahl*, Chem. Ber. *94*, 2233 (1961).

[5] We prefer the term "azenes" for the univalent derivatives of the neutral sextet-nitrogen. The name "nitrenes" used occasionally appears to the author linguistically unfavorable and misleading because it has been reserved for another class of compounds. (See Sections C1 and C 3a.)

just as undefined as in those with internal octet stabilization.

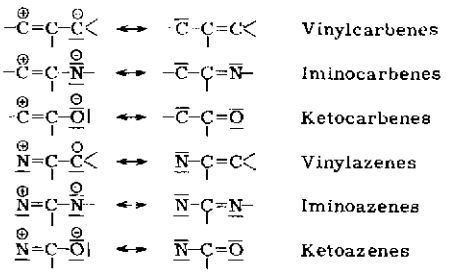
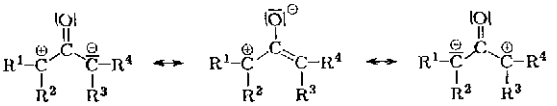


Table 3. Unsaturated carbenes and azenes as 1,3-systems

Numerous other 1,3-dipoles containing carbon as a central atom can be visualized. An "*exo*" double bond at the middle atom permits yet another type of charge interchange; the hypothetical intermediate *(3)* of the Favorski rearrangement of α-halogenoketones belongs to this type [6]. It has recently been suggested that the mechanism of the ring coupling during the formation of purpurogallin involves a variant of this zwitterion with external octet stabilization [7].



(3)

In contrast, the charges can no longer be exchanged in the systems of Table 4, in which a tetrahedral carbon is the middle atom; the sp^3-hybridized carbon acts as an insulator. Such systems can occur as short-lived intermediates and may be involved in molecular rearrangements or hydride shifts. Even though cycloadditions were undertaken with several systems of this kind and resulted in 5-membered rings, the mechanism cannot be considered as unequivocally established.

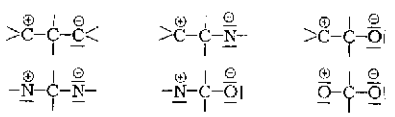


Table 4. 1,3-Dipoles without octet stabilization and with a saturated carbon atom in the middle.

The classification scheme developed up to this point does not by any means exhaust the possible structural variation of the 1,3-dipole. Inclusion of the elements of the second row of the periodic table, primarily phosphorus and sulfur, increases their number considerably. Until now, our laboratory has examined only the thioketocarbene system.

Finally there are experimental indications that elements of the groups III and VII can also participate in 1,3-dipoles. Since neutral triply bonded boron already has an electron sextet, 1,3-additions in this case probably result from another type of charge distribution. The same is true for the halogens, which, when involved in covalent bonds, cannot carry an anionic charge.

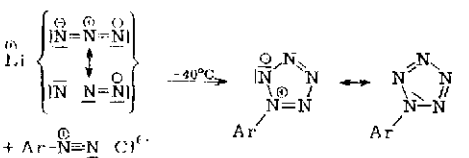
[6] *J. G. Aston* and *J. D. Newkirk*, J. Amer. chem. Soc. *73*, 3900 (1951); *J. G. Burr* and *M. J. S. Dewar*, J. chem. Soc. (London) *1954*, 1201; *H. O. House* and *W. F. Gilmore*, J. Amer. chem. Soc. *83*, 3980 (1961); *A. W. Fort*, ibid. *84*, 4979 (1962).

[7] *L. Horner*, *K. H. Weber*, and *W. Dürckheimer*, Chem. Ber. *94*, 2881 (1961).

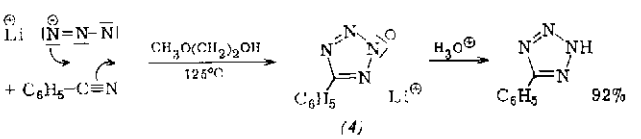
2. Some 1,3-Cycloadditions Involving Abnormally Charged Types

The product of cycloadditions proceeding according to the scheme 3 + 2 → 5 must necessarily possess a formal charge if one begins with an uncharged 1,3-dipolar system. Indeed, the disappearance of the charges in the course of the cycloaddition contributes significantly to the driving force and the energy balance of the "orthodox" 1,3-dipolar addition depicted above. Some 1,3-cycloadditions in which the charge distribution deviates from that previously encountered will now be discussed.

A simple variation from the normal cycloaddition scheme is found in the coupling of an anionic 1,3-dipolar system with a multiple bond of cationic character. The formation of arylpentazoles from aromatic diazonium ions and azide anion has been reported to proceed via a benzene diazoazide as the intermediate stage [8]. New kinetic data, however, suggest a concerted process, instead [9].

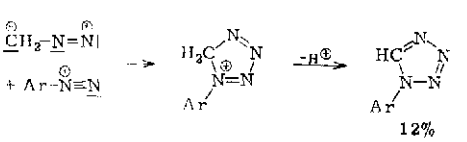


A related reaction is the addition of azide anion onto a nitrile group shown below [10]. The single-step nature of this process still remains to be confirmed experimentally. This reaction corresponds to another charge type, *viz.* addition of an anionic 1,3-dipolar system onto a neutral multiple bond system; it benefits from the mesomeric stabilization of the tetrazole anion *(4)*.



(4)

Reaction of *p*-nitrobenzenediazonium chloride with diazomethane affords, among other products, 1-(*p*-nitrophenyl)-tetrazole [11]. Here, loss of a proton may follow the 1,3-addition of a zwitterion to a cationic dipolarophile.



Even though a zwitterionic resonance structure for benzalazine has an electron deficiency and a free electron pair in the 1- and 3-positions, the charges are located at positions 1 and 2. Cycloaddition onto an uncharged

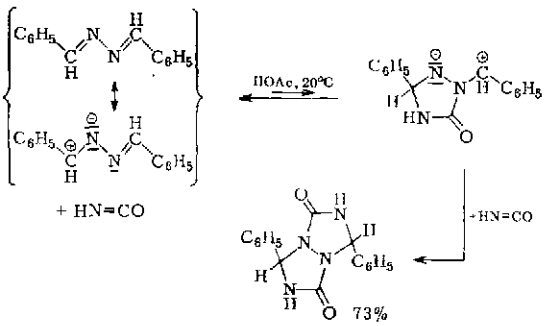
[8] *R. Huisgen* and *I. Ugi*, Chem. Ber. *90*, 2914 (1957); *I. Ugi* and *R. Huisgen*, ibid. *91*, 531 (1958).

[9] *I. Ugi*, unpublished data.

[10] *R. M. Herbst* and *K. R. Wilson*, J. org. Chemistry *22*, 1142 (1957); *W. G. Finnegan*, *R. A. Henry*, and *R. Lofquist*, J. Amer. chem. Soc. *80*, 3908 (1958); *R. Huisgen*, *J. Sauer*, *H. J. Sturm*, and *J. H. Markgraf*, Chem. Ber. *93*, 2106 (1960).

[11] *R. Huisgen* and *H. J. Koch*, Liebigs Ann. Chem. *591*, 200 (1955).

multiple bond leads necessarily to a product with formal charges and is therefore thermodynamically unfavorable. Nevertheless, such additions may take place by "trial and error". Since the zwitterionic adduct incorporates a true 1,3-dipole with normal charge distribution, cycloaddition to a second molecule of the dipolarophile terminates the process. This is a plausible mechanism for the "criss-cross addition" of cyanic acid onto benzalazine, which was described in 1917 [12]. The formation of a bis-adduct from maleic anhydride and benzalazine follows the same scheme [13].



Treatment of 2-butyne with sulfuryl chloride or with chlorine and boron trifluoride etherate yields 3,4-dichloro-1,2,3,4-tetramethylcyclobutene [14]. This unusual reaction has recently been interpreted to involve, as the critical step, the cycloaddition of a cationic 1,3-dipolar system onto the acetylenic bond to form a cyclic chloronium ion [15].

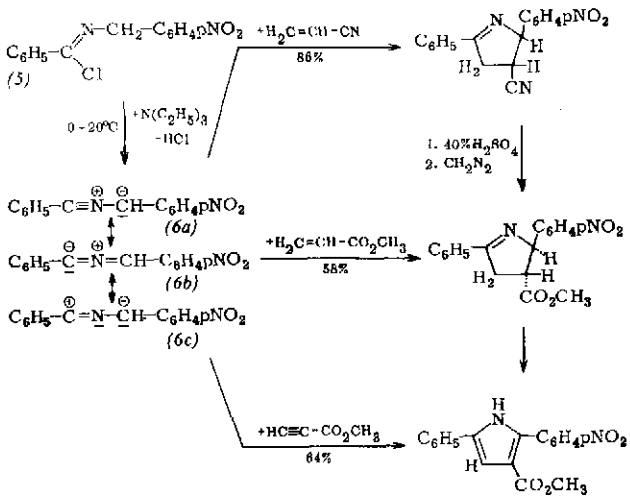
Other 1,3-cycloadditions may be identified in the reactions of alkenes with osmium tetroxide and perhaps also with the permanganate ion. These reactions lead to cyclic esters. The two electrons which are removed on closure of the two σ-bonds are taken up by the inner shells of the metal, thereby changing the oxidation state of the latter. The stereoselective *cis*-addition observed indicates a synchronous process.

Despite the close mechanistic relationship to other reactions, we consider it expedient to limit the concept of the 1,3-dipolar addition to cycloadditions of the systems presented in Tables 1 and 2.

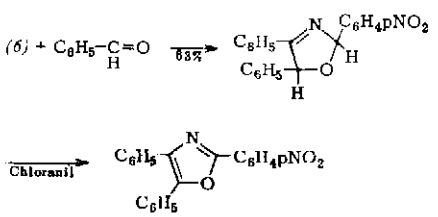
B. Additions of 1,3-Dipoles with a Double Bond and Internal Octet Stabilization

1. Nitrile Ylides

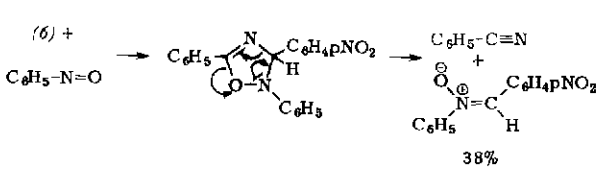
We have prepared a representative of the heretofore unknown nitrile ylides by elimination of HCl from *N*-(*p*-nitrobenzyl)benzimidoyl chloride *(5)*. Simple treatment with triethylamine in benzene at room temperature precipitates triethylammonium chloride, yielding a deep violet solution, which contains the nitrile ylide *(6)*. The latter cannot be isolated, but its 1,3-dipolar activity is demonstrated in the presence of acrylonitrile, where an 86% yield of two diastereoisomeric Δ^1-pyrrolines is obtained [16]. On acid hydrolysis, both of these compounds give the same carboxylic acid, whose methyl ester can also be prepared by addition of *(6)* onto methyl acrylate. Dehydrogenation of the Δ^1-pyrrolinecarboxylic ester with chloranil yields methyl 2-(*p*-nitrophenyl)-5-phenylpyrrole-3-carboxylate, which is identical with the adduct from methyl propiolate and the ylide *(6)*. This common orientation is the opposite of that to be expected on the basis of the nitrilium resonance formulae *(6a)* and *(6c)*. Here the principle of interchangeability of charges should be recalled.



Cycloadditions of the model substance, nitrile ylide *(6)* to phenylpropiolic ester, acetylenedicarboxylic ester, 1,4-naphthoquinone, or acenaphthylene all follow the same scheme. However, hetero-multiple bonds also add to the 1,3-dipole. Acetaldehyde and benzaldehyde afford Δ^3-oxazolines. Dehydrogenation to give oxazoles and the independent syntheses of the latter prove that here again only a single orientation exists [16].



The nitrile bond in cyanoformic ester combines with *(6)* to form an imidazole derivative. Crystalline cycloadducts are also obtainable with carbon disulfide and dithiocarboxylic esters. The addition of *(6)* onto nitroso-



[12] *J. R. Bailey* and *N. H. Moore*, J. Amer. chem. Soc. *39*, 279 (1917); *J. R. Bailey* and *A. T. McPherson*, ibid. *39*, 1322 (1917).

[13] *Th. Wagner-Jauregg*, Ber. dtsch. chem. Ges. *63*, 3213 (1930); *J. Kovacs*, *V. Bruckner*, and *I. Kandel*, Acta chim. hung. *1*, 230 (1951); *M. Häring* and *Th. Wagner-Jauregg*, Helv. chim. Acta *40*, 852 (1957).

[14] *I. V. Smirnov-Zamkov*, Dokl. Akad. Nauk SSSR *83*, 869 (1952); Chem. Abstr. *47*, 2711 (1953); *R. Criegee* and *A. Moschel*, Chem. Ber. *92*, 2181 (1959).

[15] *J. D. Roberts* and *C. M. Sharts*, Org. Reactions *12*, 1, 17 (1962).

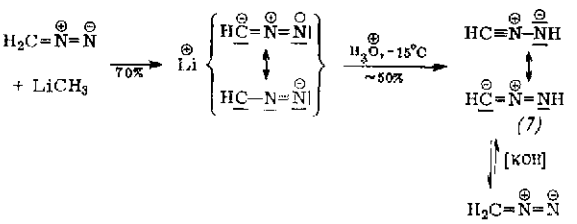
[16] *R. Huisgen*, *H. Stangl*, *H. J. Sturm*, and *H. Wagenhofer*, Angew. Chem. *74*, 31 (1962); Angew. Chem. internat. Edit. *1*, 50 (1962).

benzene also deserves mention. This is accompanied by a 1,3-elimination to give *C*-(*p*-nitrophenyl)-*N*-phenylnitrone and benzonitrile [16].

2. Nitrile Imines

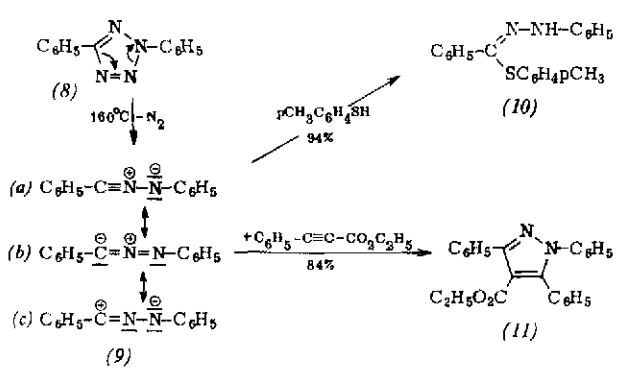
a) *Synthetic Approaches*

At the start of our investigations, only the parent compound of the series, *viz.* "isodiazomethane" *(7)*, had been described. The preparation and purification of this metastable tautomer of diazomethane is due to the experimental skill of *E. Müller* [17]. A small equilibrium concentration of the nitrile imine *(7)* has been detected spectroscopically in gaseous diazomethane [18].

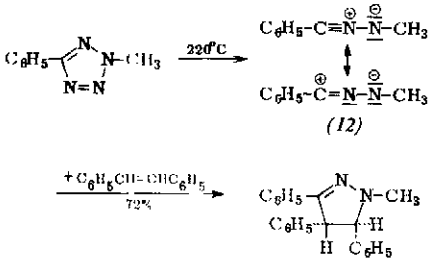


The difficult accessibility of *(7)*, its ready transformation to diazomethane, and the failure of this method even for "isodiazoethane" [19] led us to seek other syntheses, preferably of *N*-substituted nitrile imines. Acylation of 5-substituted tetrazoles yields derivatives of 1,3,4-oxadiazole via the hypothetical intermediate *N*-acyl(nitrile imines) [20]. This suggested the possibility of obtaining nitrile imines by thermolysis of 2,5-disubstituted tetrazoles. One mole of nitrogen is in fact liberated on heating 2,5-diphenyltetrazole *(8)* in *p*-thiocresol at 160 °C. The [α-(*p*-tolylmercapto)benzal]-phenylhydrazine *(10)* which can be isolated in 94 % yield is formed by addition of the thiol to diphenyl-(nitrile imine) *(9)* [21].

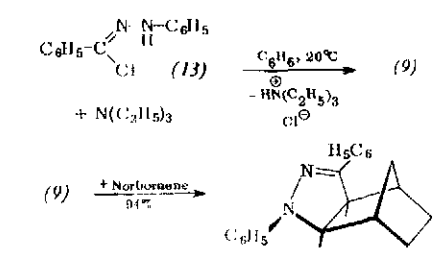
If decomposition of the tetrazole *(8)* is carried out in ethyl phenylpropiolate, the adduct *(11)* is obtained in 84 % yield. The latter can be converted into the known 1,3,5-triphenylpyrazole [22]. The decomposition of diphenyltetrazole follows first-order kinetics, with a rate nearly independent of the nature of the solvent [23]. This precludes an interaction with the medium prior to elimination of the nitrogen molecule and confirms that the nitrile imine is an intermediate.



Alkylated tetrazoles also undergo elimination of nitrogen on heating. With 2-methyl-5-phenyltetrazole, however, thermolysis does not occur below about 220 °C, and proceeds in competition with a second decomposition route which leads to benzonitrile and methyl azide. Nevertheless, cycloaddition of *C*-phenyl-*N*-metbyl(nitrile imine) *(12)* onto *trans*-stilbene is accomplished smoothly [24].



The high temperature required for the opening of the aromatic tetrazole nucleus is a serious disadvantage and restricts the choice of the dipolarophile. In the search for better synthetic methods, it was found that treatment of carboxylic acid hydrazide halides with bases proves to be a superior method because it allowed the liberation of nitrile imines even at room temperature [22, 25]. The action of triethylamine on *N*-(α-chlorobenzylidene)-*N'*-phenylhydrazine *(13)*, which is readily accessible from *N*-benzoyl-*N'*-phenylhydrazine and phosphorus pentachloride, results in 1,3-elimination of hydrogen chloride. In the presence of ethyl phenylpropiolate, an 86 % yield of the same crystalline ethyl 1,3,5-triphenylpyrazole-4-carboxylate *(11)* is obtained. This indicates that diphenyl(nitrile imine) *(9)* is the common intermediate. In an analogous manner, addition of *(9)* onto norbornene affords a bridged *exo*-Δ²-pyrazoline [22]. The configuration was established beyond doubt by comparison of the nuclear magnetic resonance spectrum with that of the pertinent *endo*-isomer [26].



[17] *E. Müller* and *W. Kreutzmann*, Liebigs Ann. Chem. *512*, 264 (1934); *E. Müller* and *D. Ludsteck*, Chem. Ber. *87*, 1887 (1954).

[18] *J. M. Mills* and *H. W. Thompson*, Trans. Faraday Soc. *50*, 1270 (1954).

[19] *E. Müller* and *W. Rundel*, Chem. Ber. *89*, 1065 (1956).

[20] *R. Huisgen, J. Sauer, H. J. Sturm*, and *J. H. Markgraf*, Chem. Ber. *93*, 2106 (1960).

[21] *R. Huisgen, J. Sauer*, and *M. Seidel*, Chem. Ber. *94*, 2503 (1961).

[22] *R. Huisgen, M. Seidel, G. Wallbillich*, and *H. Knupfer*, Tetrahedron *17*, 3 (1962).

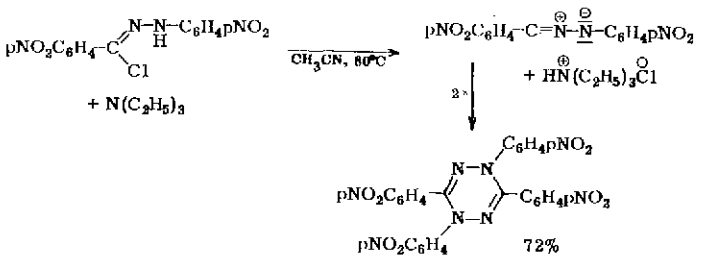
[23] *R. Huisgen, R. Grashey, M. Seidel, G. Wallbillich, H. Knupfer*, and *R. Schmidt*, Liebigs Ann. Chem. *653*, 105 (1962).

[24] *M. Seidel*, Ph.D. Thesis, Universität München, 1960.

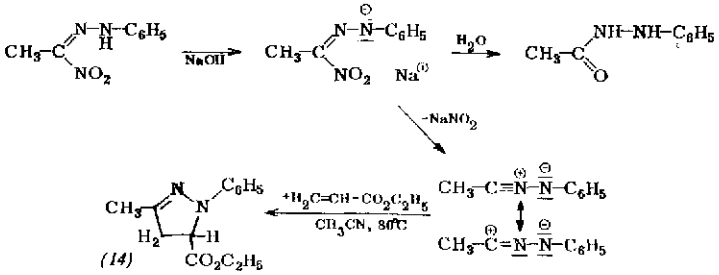
[25] *R. Huisgen, M. Seidel, J. Sauer, J. W. McFarland*, and *G. Wallbillich*, J. org. Chemistry *24*, 892 (1959).

[26] *G. Wallbillich* and *E. Spindler*, unpublished results, München, 1962.

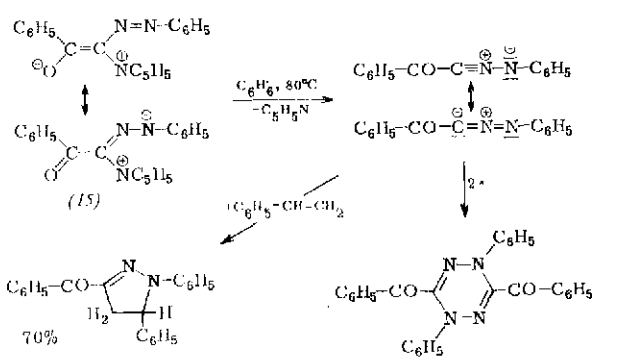
Attempts to isolate diphenyl(nitrile imine) or its nuclear-substituted derivatives have thus far failed. The reactivity of the nitrile imines is so great that, in contrast to the isomeric diazoalkanes, they react at once with each other if there is no other coreactant available. "Head-to-tail" dimerization to give a derivative of 1,4-dihydro-1,2,4,5-tetrazine is illustrated below with di-*p*-nitrophenyl(nitrile imine) [27].



Other routes are closely related. According to *E. Bamberger* [28], α-nitroacetaldehyde phenylhydrazone (obtained by azo coupling of nitroethane with benzenediazonium chloride) gives a sodium salt which yields *N*-acetyl-*N'*-phenylhydrazine when heated in aqueous alcohol. The supposition that *C*-methyl-*N*-phenyl(nitrile imine) occurs as the intermediate was shown to be correct. On heating the sodium salt with ethyl acrylate in acetonitrile, an 85 % yield of the pyrazoline *(14)* was obtained [27]. C-Alkylated nitrile imines are readily accessible in this manner.

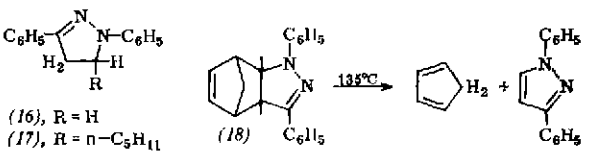


Hydrazidoyl chlorides of α-keto acids, which are prepared from β-dicarbonyl compounds by azo coupling and chlorination (the reverse sequence is also possible) [29], lead to *C*-acylnitrile imines. An experiment by *F. Krollpfeiffer* is worthy of mention here. On heating, the "pyridinium enol betaine" *(15)* suffers loss of pyridine and affords a dihydrotetrazine derivative [30], which in a formal sense may be considered as the dimer of *C*-benzoyl-*N*-phenyl(nitrile imine). That this intermediate actually occurs is suggested by the trapping reaction in the presence of styrene [31].



b) *1,3-Additions to Alkenes and Alkynes*

Some examples of the formation of Δ²-pyrazolines from nitrile imines and alkenes have already been cited above. If a benzene solution of *N*-(α-chlorobenzylidene)-*N'*-phenylhydrazine *(13)* and triethylamine is shaken in an atmosphere of ethylene, an 81 % yield of 1,3-diphenyl-Δ²-pyrazoline *(16)* is obtained [32]. Other olefins such as 1-heptene [85 % adduct *(17)*], isobutylene (74 %), and 2-butene react analogously, but the cycloaddition fails with tri- and tetraalkylated ethylenes. Cyclopentene adds to diphenyl(nitrile imine) more readily than does cyclohexene. Most of these alkenes do not react with the isomer of *(9)*, *viz.* the well-known diphenyldiazomethane. This serves to emphasize the superiority of the nitrile imines as 1,3-dipoles.

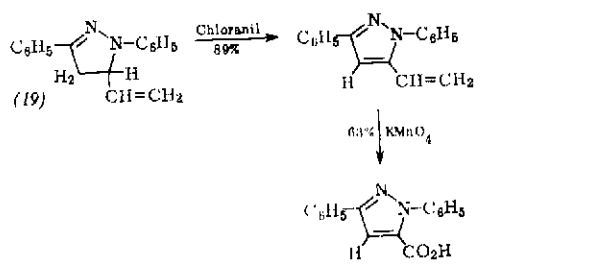


(16), R = H
(17), R = n-C_5H_{11}

Addition of *(9)* to the angularly strained double bond of bicyclo[2.2.1]heptene and its derivatives takes place very readily. With norbornadiene, *(9)* gives a 79 % yield of the mono-adduct *(18)*. However, concurrent formation of a bis-adduct (6 %) cannot be suppressed even with a 12-fold excess of the reagent. The mono-adduct decomposes completely at the melting point in a reverse Diels-Alder reaction, yielding cyclopentadiene and 1,3-diphenylpyrazole [22].

Any type of conjugation increases the activity of the olefinic dipolarophile. This phenomenon, which is characteristic of all 1,3-dipolar additions, was not expected a priori, insofar as the conjugation energy of the alkene is lost in the course of the addition because the olefinic sp^2 centers become tetrahedral.

Reaction of butadiene with *N*-(α-chlorobenzylidene)-*N'*-phenylhydrazine *(13)* and triethylamine in benzene at 20 °C gives a 94 % yield of 1,3-diphenyl-5-vinyl-Δ²-pyrazoline *(19)*; conversion of the latter into 1,3-diphenyl-



[27] *H. Knupfer*, Ph.D. Thesis, Universität München, 1963.

[28] *E. Bamberger*, Ber. dtsch. chem. Ges. *31*, 2626 (1898).

[29] *D. A. Bowack* and *A. Lapworth*, J. chem. Soc. (London) *87*, 1854 (1905); *C. Bülow* and *P. W. Neber*, Ber. dtsch. chem. Ges. *45*, 3732 (1912); *46*, 2370 (1913); *49*, 2179 (1916); *P. W. Neber* and *H. Wörner*, Liebigs Ann. Chem. *526*, 173 (1936).

[30] *F. Krollpfeiffer* and *E. Braun*, Ber. dtsch. chem. Ges. *70*, 89 (1937).

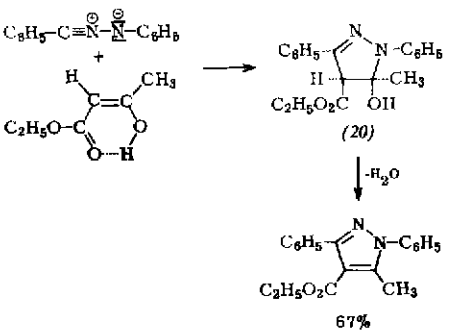
[31] *H. Hauck*, Diploma Thesis, Universität München, 1961, and unpublished results.

[32] *V. Weberndörfer*, Diploma Thesis, Universität München, 1961.

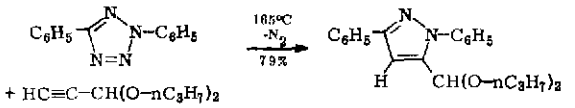
pyrazole-5-carboxylic acid confirms the direction of addition [22].

On addition of diphenyl(nitrile imine) to styrene (88 % adduct) or to 1,2-dihydronaphthalene (84 %), the aryl residue appears at position 5 of the Δ^2-pyrazoline as does the vinyl residue in the butadiene addition mentioned above [22]. Acrylic ester and fumaric ester take up nitrile imines with exceptional ease. This conclusion is based not only on the 99 % yield of adduct from the reaction of dimethyl fumarate and *(9)*, but also on the results of competition experiments with mixtures of dipolarophiles. These experiments show that *(9)* adds onto dimethyl fumarate 177 times faster than to styrene, and onto ethyl acrylate 30 times faster than to styrene [26]. The activating power of the neighboring carboxylic ester function is so large that one still obtains 94 % of the diphenyl(nitrile imine) adduct with tetraethyl ethylenetetracarboxylate, even though the accumulation of bulky groups at the dipolarophilic double bond results in considerable steric hindrance. This hindrance is manifested in a decrease in the rate of addition by a factor of 310, compared with fumaric ester. However, a 74 % yield of adduct can be obtained even with dimethyl *trans*-2-butene-2,3-dicarboxylate [22].

Although acrylic ester and acrylonitrile lead exclusively to 5-substituted Δ^2-pyrazolines, decomposition of *(8)* in acetoacetic ester at 165 °C results in a 67 % yield of ethyl 1,3-diphenyl-5-methylpyrazole-4-carboxylate. The primary Δ^2-pyrazoline *(20)* spontaneously ejects water and aromatizes to the pyrazole [22]. It may be deduced that the addition of *(9)* to the enol double bond proceeds with an orientation, relative to the carboxylic ester group, which is opposite to that observed in acrylic ester. More than 20 years ago, *R. Fusco* also prepared 5-membered heterocycles from α-halogenoalkylidene hydrazines and the alkali salts of CH-acidic compounds [33].

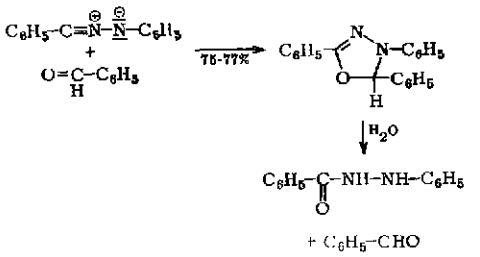


Addition of diphenyl(nitrile imine) to a C≡C triple bond yields the aromatic pyrazole system directly [22]. The effect of substituents on the dipolarophilic activity of the triple bond is similar to that indicated above for the double bond. The formation of 1,3,5-triphenylpyrazole from phenylacetylene and *(9)* is an example pertinent. All monosubstituted acetylenes yield 5-substituted pyrazoles [22].



c) *C=O and C=S Double Bonds as Dipolarophiles*

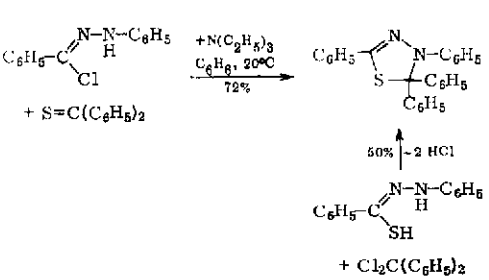
The ability to add nitrile imines is not restricted to CC multiple bonds. Thus, the C=O group may act as a dipolarophile. For example, with benzaldehyde *(9)* always yields 2,4,5-triphenyl-1,3,4-oxadiazoline, a representative of a ring system not previously described [34], regardless of whether *N*-(α-chlorobenzylidene)-*N'*-phenylhydrazine at 80 °C or the thermolysis of diphenyltetrazole at 160 °C is used as the source of *(9)*. The cyclic α-amino ether formed is susceptible to hydrolysis even in warm aqueous methanol.



The dipolarophilic activity of carbonyl compounds is not especially great; for example, normal ketones do not react with *(9)*. In contrast, the electron-deficient carbonyl groups of benzil or of diethyl mesoxalate afford 75 and 73 %, respectively, of the diphenyl(nitrile imine) adduct.

When one considers that the mechanisms of the Diels-Alder synthesis and of the 1,3-dipolar cycloaddition reaction are closely related, the conclusion might follow that good dienophiles should also be active dipolarophiles, and vice versa. However, a difference between these functions is demonstrated, for example, by the behavior of the C=S double bond, which exhibits only slight dienophilic character. As a dipolarophile, however, the C=S double bond has unusually great activity. Thiobenzophenone reacts with diphenyl(nitrile imine) to form the tetraphenyl derivative of Δ^2-1,3,4-thiadiazoline, which has also been synthetized independently [34].

The great readiness of thionamides, thionecarboxylic esters and thionecarbamic esters to undergo addition is

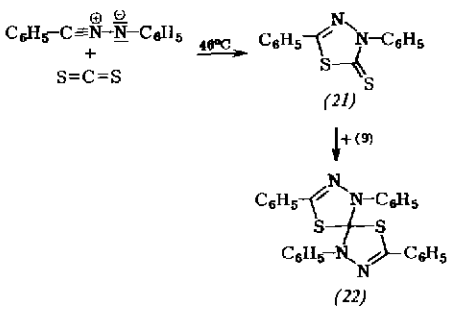


[33] *R. Fusco* and *R. Justoni*, Gazz. chim. ital. *67*, 3 (1937); *R. Justoni*, ibid. *68*, 49 (1938); *R. Fusco*, ibid. *69*, 344, 353, 364 (1939); *72*, 411 (1942); *R. Fusco* and *R. Romani*, ibid. *76*, 419, 439 (1946); *78*, 342 (1948); *V. Evdokimoff*, ibid. *87*, 1191 (1957). See also *P. Grünanger* and *M. R. Langella*, ibid. *90*, 229 (1960).

[34] *R. Huisgen*, *R. Grashey*, *M. Seidel*, *H. Knupfer*, and *R. Schmidt*, Liebigs Ann. Chem. *658*, 169 (1962).

quite surprising. In normal thioesters, where the alkyl residue is attached to sulfur, the mesomerism of carboxylic esters is suppressed to such an extent (owing to the slight tendency of sulfur to participate in double bonds) that these compounds acquire the character of acylating agents. For the same reason, an especially high degree of single bond character would be expected in the C=S double bond of thione esters and thionamides. Nevertheless, these compounds add diphenyl(nitrile imine) with unusual ease, perhaps as a result of the high polarizability of the sulfur function.

Liberation of *(9)* from precursors dissolved in carbon disulfide leads, despite the excess of the sulfur compound present, to a 63 % yield of a 2:1 adduct *(22)*, which embodies a new type of system, *viz.* 5,5-spirobi-1,3,4-thiadiazoline. The second addition step is obviously faster than the first. The primary adduct *(21)*, which is a cyclic dithiourethane and which was prepared by an independent method, affords the spirane *(22)* quantitatively on further reaction with *(9)* [34].

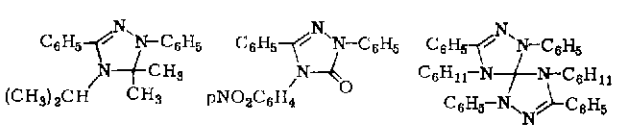


(21) *(22)*

Phenyl isothiocyanate displays comparable dipolarophilic activity in both of its double bonds. Monoadducts are obtained with diphenyl(nitrile imine) at both the C=S and C=N double bonds, in yields of 58 % and 29 %, respectively [34].

d) *Additions to CN Double and Triple Bonds*

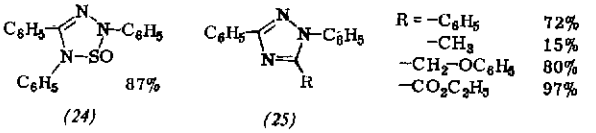
Aliphatic and aromatic azomethines (Schiff bases) are able to add nitrile imines; their dipolarophilic character is considerably more pronounced than that of the parent carbonyl compound. Although acetone itself fails to add diphenyl(nitrile imine), acetone-*N*-isopropylimine gives the adduct *(23)* in 84 % yield. This may be the easiest synthetic route to the 1,2,4-Δ^2-triazoline series [35].



(23) 88% 46%

The same relative orientation towards the C=N double bond is observed in the addition of diphenyl(nitrile imine) to isocyanates and carbodiimides. The cumulated system of the carbodiimide is an inferior acceptor relative to the guanidine group found in the monoadduct. Thus, just as in the case of carbon disulfide, only the bis-adduct can be obtained. Examples formulated above are reactions with *p*-nitrophenyl isocyanate and dicyclohexylcarbodiimide [35].

Finally, although it is not strictly pertinent here, the dipolarophilic activity of the S=N double bond of *N*-sulfinylaniline is noteworthy; the ring system in the adduct *(24)* is new. Diels-Alder additions of *N*-sulfinylarylamines have been reported [36].



(24) 87% *(25)* R = $-C_6H_5$ 72%; $-CH_3$ 15%; $-CH_2-OC_6H_5$ 80%; $-CO_2C_2H_5$ 97%

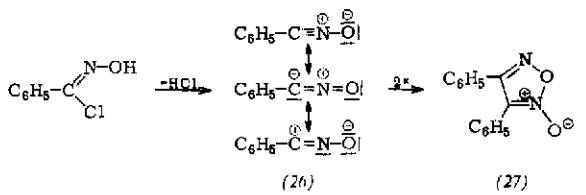
The interaction of nitrile imines with nitriles permits synthesis of 1,2,4-triazoles *(25)*. The C≡N triple bond is less active than the C≡C triple bond. Although aromatic nitriles react satisfactorily with *(13)* and triethylamine, the yield falls in the reaction with acetonitrile. It rises once more to better than 70 %, with α-methoxy- or α-phenoxyacetonitrile as well as with cyanoformic ester [23].

All additions to hetero-double or -triple bonds occur in the direction which involves a maximum gain in σ bond energy. Formation of a bond between the nitrile imine nitrogen and a nitrogen, oxygen, or sulfur atom of the dipolarophile is energetically unfavorable and therefore does not occur if other alternatives exist.

3. Nitrile Oxides

a) *Preparation and Dimerization*

Benzhydroxamic acid chloride (α-hydroxyiminobenzyl chloride), is obtained by chlorination of benzaldoxime and affords benzonitrile-*N*-oxide *(26)* on treatment with sodium carbonate solution. The nitrile oxide dimerizes spontaneously to diphenylfuroxan *(27)* [37,38]. The formation of furoxans is a characteristic property of the nitrile oxides and can feasibly be regarded as a 1,3-dipolar addition of one molecule of nitrile oxide onto the CN bond of another, the latter acting as a dipolarophile. The orientation, however, conflicts with the principle set forth in the previous paragraph. There are good reasons to interpret this dimerization in a different way.



(26) *(27)*

Benzonitrolic acid, which is prepared from phenylnitromethane and nitrous acid, loses HNO_2 readily, and may thus

[35] *R. Huisgen, R. Grashey, H. Knupfer, M. Seidel*, and *R. Schmidt*, Chem. Ber., in the press.

[36] *O. Wichterle* and *J. Rocek*, Chem. Listy *47*, 1768 (1953); *G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H. P. Patzschke, H. Smalla*, and *A. Trede*, Angew. Chem. *74*, 135 (1962); Angew. Chem. internat. Edit. *1*, 89 (1963).

[37] *A. Werner* and *H. Buss*, Ber. dtsch. chem. Ges. *27*, 2193 (1894).

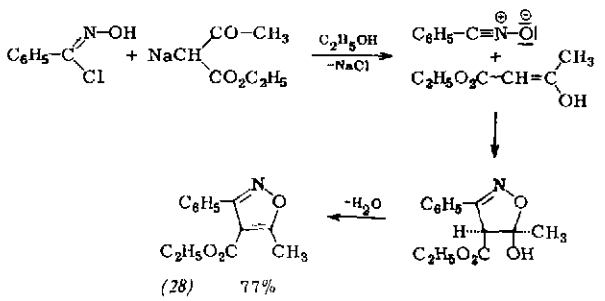
[38] *H. Wieland*, Ber. dtsch. chem. Ges. *40*, 1667 (1907).

serve as a source of benzonitrile-*N*-oxide [39]. This preparation is reminiscent of that of fulminic acid from methylnitrolic acid or from ethanol and nitric acid. Indeed, the structure of a formonitrile oxide accounts so well for the properties, particularly the polymerization, of fulminic acid [40] that the existence of a compound C=NOH appears to be questionable.

An elegant route leading to aliphatic nitrile oxides, which has recently been discovered, involves interaction of isocyanates and tertiary amines with nitroalkanes [41]. The acylation product of the *aci*-nitro compound undergoes an E_2 elimination under the influence of base. The dimerization, *e.g.* of acetonitrile oxide, follows so rapidly that it is necesary to study combinations with other reactants *in situ*.

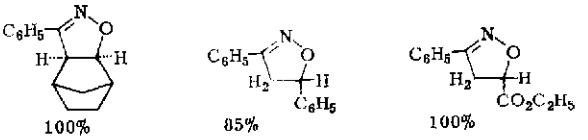
b) *1,3-Additions to Alkenes and Alkynes*

A. Quilico and *R. Fusco* obtained the isoxazole derivative *(28)* from sodio-acetoacetic ester and benzhydroxamic acid chloride. The reaction was formulated as proceeding by way of the corresponding carbanion, via primary nucleophilic substitution of the chlorine and subsequent cyclization [42]. Numerous other activc methylene compounds react analogously [43]. Only later, when benzonitrile oxide was recognized as the intermediate [44], was the way open for the investigation of the addition of nitrile oxides to alkenes incapable of anion formation.



(28) 77%

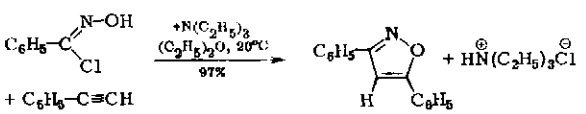
A. Quilico and his school added nitrile oxides onto various types of alkenes to form Δ^2-isoxazolines. Normally the nitrile oxide was liberated from the hydroxamic acid chloride with aqueous alkali, taken up in ether, and treated with the olefin [45]. We found that the interfering dimerization to furoxan could be effectively suppressed by working with low stationary concentrations of the nitrile oxide. Slow addition of triethylamine to an ethereal solution of the hydroxamic acid chloride and a dipolarophile favors combination with the alkene [46]. Yields of 80–100 % are common when operating in this manner. The additions of benzonitrile oxide onto norbornene, styrene, and ethyl acrylate may serve as examples.



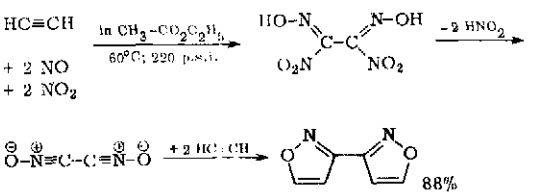
100% 85% 100%

Monosubstituted or 1,1-disubstituted ethylenes always yield 5-substituted Δ^2-isoxazolines. Tri- and tetraalkylethylenes are no longer capable of addition. Allene, which reacts sluggishly, yields a bis-adduct [47]. The dipolarophilic activity of cyclopentene is higher than that of cyclohexene; unlike *(9)*, *(26)* no longer combines with cyclohexene [45]. Aliphatic nitrile oxides undergo corresponding additions [41].

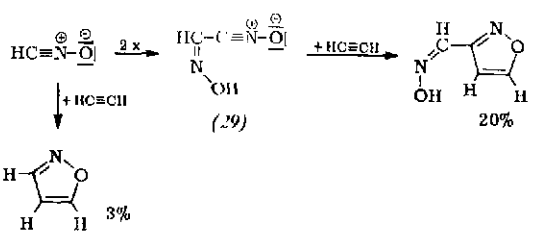
The reaction of nitrile oxides with alkynes leads to aromatic isoxazoles. The advantage of the "dilution method" described above, where the stationary concentration of nitrile oxide is kept low, is proven here as well, resulting in yields exceeding 90 % [46]. In another procedure, *viz.* reaction of alkynylmagnesium halides with hydroxamic acid chlorides, it is likely that the nitrile oxide is also an intermediate [44,48].



A novel and fruitful synthesis of 3,3'-bis(isoxazolyl) from acetylene and nitrous gases presumably proceeds by way of a twofold 1,3-dipolar addition of cyanogen-*N*,*N*'-dioxide [49].



Addition of formonitrile oxide, liberated *in situ*, to acetylene or phenylacetylene is complicated by the competing polymerization of the 1,3-dipole. The for-



(29) 20% 3%

[39] *H. Wieland* and *L. Semper*, Ber. dtsch. chem. Ges. *39*, 2522 (1906).

[40] *H. Wieland, A. Baumann, C. Reisenegger, W. Scherer, J. Thiele, J. Will, H. Haussmann*, and *W. Frank*, Liebigs Ann. Chem. *444*, 7 (1925).

[41] *T. Mukaiyama* and *T. Hoshino*, J. Amer. chem. Soc. *82*, 5339 (1960).

[42] *A. Quilico* and *R. Fusco*, Gazz. chim. ital. *67*, 589 (1937).

[43] *L. Panizzi*, Gazz. chim. ital. *69*, 322 (1939); *70*, 89, 119 (1940); *C. Musante*, ibid. *69*, 523 (1939).

[44] *A. Quilico* and *G. Speroni*, Gazz. chim. ital. *76*, 148 (1946).

[45] *A. Quilico, G. Stagno d'Alcontres*, and *P. Grünanger*, Gazz. chim. ital. *80*, 479 (1950); *A. Quilico* and *P. Grünanger*, ibid. *82*, 140 (1952); *A. Quilico, P. Grünanger*, and *R. Mazzini*, ibid. *82*, 349 (1952); *G. Stagno d'Alcontres*, ibid. *82*, 627 (1952); *N. Barbalescu, P. Grünanger, M. R. Langella*, and *A. Quilico*, Tetrahedron Letters *1961*, 89.

[46] *R. Huisgen, W. Mack, E. Anneser*, and *K. Herbig*, unpublished results, München, 1960/61.

[47] *G. Stagno d'Alcontres* and *G. Lo Vecchio*, Gazz. chim. ital. *90*, 1239 (1960).

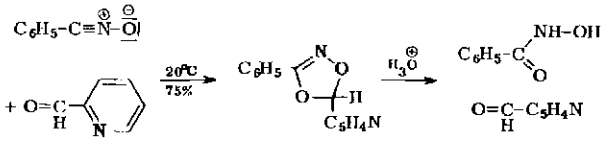
[48] *A. Quilico* and *G. Stagno d'Alcontres*, Gazz. chim. ital. *79*, 703 (1949); *E. Magnani* and *P. Grünanger*, Atti Accad. Naz. Lincei (8) *14*, 95 (1953); *A. Quilico, G. Gaudiano*, and *A. Ricca*, Gazz. chim. ital. *87*, 638 (1957); Tetrahedron *7*, 24 (1959); *P. Grünanger* and *M. R. Langella*, Gazz. chim. ital. *89*, 1784 (1959).

[49] *R. Cramer* and *W. R. McClellan*, J. org. Chemistry *26*, 2976 (1961); cf. *C. Grundmann*, Angew. Chem. *75*, 450 (1963); Angew. Chem. internat. Edit. *2*, 309 (1963).

mation of isoxazole-3-aldoxime demonstrates that the dimer of fulminic acid, postulated by *H. Wieland* [40] to be hydroximino-acetonitrile-*N*-oxide *(29)*, is trapped by acetylene through a 1,3-addition [48].

c) *Reactions with Carbonyl Compounds and Azomethines*

Aromatic aldehydes add nitrile oxides across the C=O double bond, thus providing a synthetic route to 1,3,4-dioxazoles [50]. Previously, the 2-keto derivatives were the only representatives of this ring system described in the literature. The nitrile oxides should not be liberated prior to the introduction of the carbonyl compound. 1,3,4-Dioxazoles exhibit the same infrared CN vibration as imido esters and like cyclic acetals they undergo hydrolysis in acidic solution.

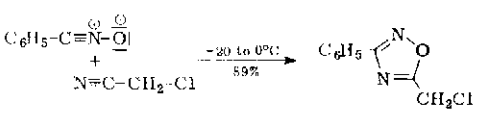


Although acetaldehyde, acetophenone, and γ-butyrolactone do not undergo additions with benzonitrile oxide, the latter does react with chloral (44 % adduct), ethyl glyoxylate (67 %), ethyl pyruvate (91 %), biacetyl (65 %), and diethyl mesoxalate (75 %) [50]. Similar relationships are described in Section B 2c concerning the addition of nitrilimines.

The reaction of nitrile oxides with azomethines is subject to much less limitation. This addition leads to the Δ^2-1,2,4-oxadiazoline series; for example, ethylidene-n-butylamine, benzalaniline, and furfurylidenemethylamine form adducts with benzonitrile oxide in yields of 94 %, 78 %, and 84 %, respectively [51].

d) *Additions to Nitriles*

The addition to the C≡N triple bond is of somewhat less preparative interest since 1,2,4-oxadiazoles may also be obtained by other routes. The specificity is similar to that exhibited towards diphenylnitrilimine (see Section B 2d). Benzonitrile oxide combines with the aromatic cyano group [52, 53], whereas aliphatic nitriles form adducts only when they bear electron-attracting substituents; these include (with adduct yield) benzoyl cyanide (61 %), acetyl cyanide (68 %), ethyl cyanoformate (71 %), cyanogen (73 %), phenoxyacetonitrile (62 %), and chloroacetonitrile (89 %) [53].



[50] *R. Huisgen* and *W. Mack*, Tetrahedron Letters *1961*, 583.

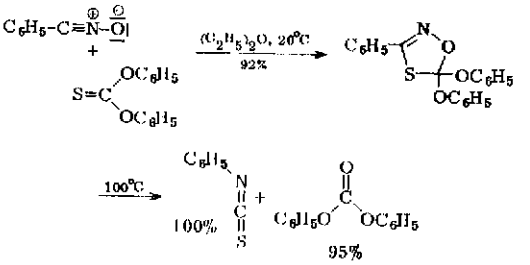
[51] *R. Huisgen, W. Mack, K. Herbig*, and *K. Bast*, unpublished results, München, 1961/63.

[52] *G. Leandri* and *M. Pallotti*, Ann. Chim. (Roma) *47*, 376 (1957); Chem. Abstr. *51*, 15 502 (1957).

[53] *R. Huisgen, W. Mack*, and *E. Anneser*, Tetrahedron Letters *1961*, 587.

e) *Dipolarophilic Thiocarbonyl Compounds*

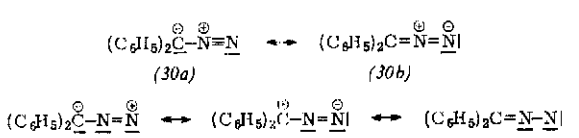
Aromatic and aliphatic nitrile oxides add readily and in good yield onto thioketones, thionecarboxylic esters, dithiocarboxylic esters, thionecarbonates, and trithiocarbonates [54]. This cycloaddition is attractive for reasons other than the mere fact that the 1,4,2-oxathiazoles so produced are new (only the 3-phenyl-5-imino compound has been described in the literature). With the exception of the 3,5,5-triphenyl derivative, all the 1,4,2-oxathiazoles studied decompose exothermically at 90–150 °C to form isothiocyanates and the oxygen analogues of the starting thiocarbonyl compounds. The molecular rearrangement leading to the isothiocyanate probably proceeds concurrently with the ring opening, since a thioketoazene intermediate could not be intercepted.



In the case of the thionamides and thioureas, the corresponding cleavage follows the 1,3-addition even at room temperature. Thus treatment of *p*-nitrobenzonitrile oxide with *N,N*-dimethylthionebenzamide yields 87 % *p*-nitrophenyl isothiocyanate and 90 % *N,N*-dimethylbenzamide [54]. An adduct made from benzonitrile oxide and *N*-sulfinylaniline has recently been reported [55].

4. Diazoalkanes

The preparative significance and intensive study of this class of compounds are reflected in the extensive literature on the subject. The old cyclic formula for the diazoalkanes was replaced as early as 1911 with the open chain structure by *A. Angeli* and *J. Thiele*. This was later corroborated by physical data. The aliphatic diazo compounds, which appear in the classification of 1,3-dipoles (Table 1) as diazonium ylides, show the characteristic ground state charge compensation, caused by the mesomerism of the two all-octet formulae. While a dipole moment of 6.4 D would be expected for an electron distribution corresponding to *(30a)*, diphenyldiazomethane actually has a value of 1.42 D (benzene, 25 °C) [56]. Reduction of the moment to 0.62 D in the *p,p'*-dichloro derivative shows that a greater weight of structure *(30b)* determines the direction of the electric moment.



Unlike the nitrilium betaines, the diazonium betaines can be isolated and some are even thermally stable.

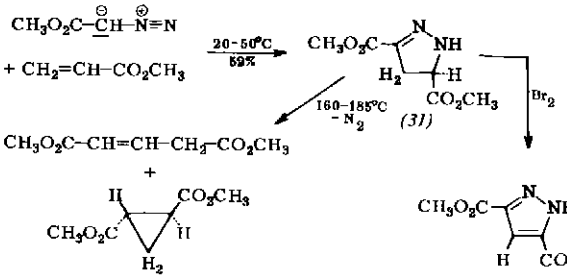
[54] *R. Huisgen, W. Mack*, and *E. Anneser*, Angew. Chem. *73*, 656 (1961).

[55] *P. Rajagopalan* and *H. U. Daeniker*, Angew. Chem. *75*, 91 (1963); Angew. Chem. internat. Edit. *2*, 46 (1963).

[56] *N. V. Sidgwick, L. E. Sutton*, and *W. Thomas*, J. chem. Soc. (London) *1933*, 406.

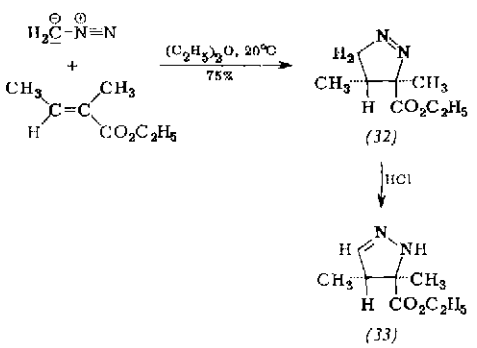
a) *1,3-Addition to Alkenes*

Only six years after the discovery of diazoacetic ester by *Th. Curtius* in 1883, *E. Buchner* described its addition onto α,β-unsaturated carboxylic esters [57]. He recognized the adduct obtained from methyl diazoacetate and acrylic ester as dimethyl Δ²-pyrazoline-3,5-dicarboxylate *(31)*. Dehydrogenation by bromine and thermolysis to yield glutaconic ester and *trans*-1,2-cyclopropanedicarboxylic ester established the direction of addition.

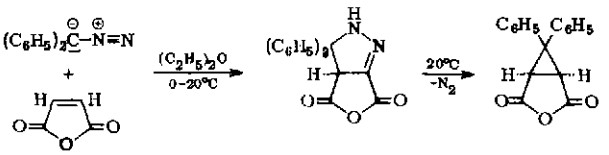


This synthetic route to pyrazolines and cyclopropanes was used so frequently thereafter [58] that there is room here to review only a few characteristics. The facility of addition of the diazo compounds decreases in the sequence: diazomethane > diphenyldiazomethane > diazoacetic ester > diazoketones > α-diazo-β-dicarbonyl compounds.

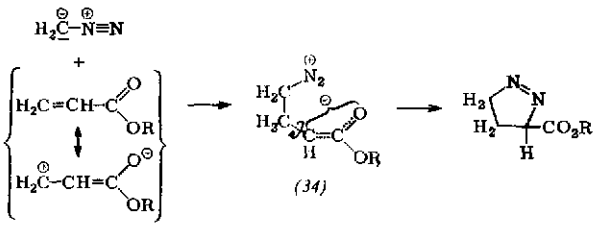
The initial products of addition of diazoalkanes are Δ¹-pyrazolines, which mostly isomerize rapidly to the carbonyl-conjugated Δ²-pyrazolines. The adduct formed by stereospecific *cis*-addition between diazomethane and tiglic ester lacks the acidic α-hydrogen of the carboxylic ester. Thus, the Δ¹-pyrazoline *(32)* can be isolated and is transformed into the Δ²-tautomer *(33)* only in acidic medium [59, 60]. The evolution of nitrogen which occurs above 100 °C yields *cis*- and *trans*-1,2-dimethylcyclopropane-2-carboxylic esters in a ratio of 1.0:0.7, and thus does not proceed stereoselectively. Likewise, the formation of trimethylacrylic ester is consistent with an open chain zwitterionic intermediate [60].



The adducts obtained from diphenyldiazomethane with α,β-unsaturated carbonyl compounds lose nitrogen at even lower temperatures. The pyrazoline derived from maleic anhydride slowly yields the cyclopropane derivative at 20 °C, probably via the Δ¹-tautomer [61]. Frequently the rate of evolution of nitrogen exceeds even that of the addition; in particular, this is known to be the case for diazofluorene. However, there is no reason to postulate a change in mechanism, as long as the rate of addition is greater than that of the decomposition of the diazoalkane. The mechanism of this synthetic route to cyclopropanes via pyrazolines must be carefully distinguished from that of the addition of carbenes onto unsaturated compounds.



In all of these additions the nucleophilic diazoalkane carbon forms a bond with the electrophilic β-position of the α,β-unsaturated carboxylic ester, ketone, or nitrile. This orientation led to the assumption that the addition occurs in two steps, with a kind of intramolecular azo coupling as the concluding step [62].



The stereoselectivity of the addition of diazoalkanes onto *cis-trans* isomeric alkenes, in *(32)* formulated for tiglic ester, introduces some doubt as to the validity of the two-step addition mechanism, for in the intermediate *(34)* the original olefinic double bond becomes capable of free rotation and this should impair the stereoselectivity.

1,3-Butadiene adds on diazomethane [63]; styrene and diphenyldiazomethane give 60 % 1,1,2-triphenylcyclopropane via the pyrazoline. The pyrazolines obtained from cyclopentene with diphenyldiazomethane or diazoacetic ester are even stable [64]. It is to be noted that these olefins are not electrophilic. Other instances in which the orientation principle cited above is violated constitute still stronger arguments against the occurrence of *(34)* as an intermediate. In contrast to diazoacetic ester, diphenyldiazomethane adds "abnormally" to 1-aryl-2-nitroethylenes [65]. The interaction of diazomethane with styryl methyl sulfone likewise yields more of the abnormal than of the normal adduct [66].

[57] *E. Buchner*, Ber. dtsch. chem. Ges. *21*, 2637 (1888); *23*, 701 (1890); *E. Buchner* and *A. Papendieck*, Liebigs Ann. Chem. *273*, 232 (1893).

[58] Reviews: *R. Huisgen*, Angew. Chem. *67*, 439 (1955); *T. L. Jacobs* in *R. C. Elderfield:* Heterocyclic Compounds. Wiley, New York 1957, Vol. 5, p. 72; *H. Zollinger:* Azo and Diazo Chemistry. Interscience, New York 1961.

[59] *K. v. Auwers* and *F. König*, Liebigs Ann. Chem. *496*, 27 (1932).

[60] *T. V. v. Auken* and *K. L. Rinehart*, J. Amer. chem. Soc. *84*, 3736 (1962).

[61] *J. v. Alphen*, Rec. Trav. chim. Pays-Bas *62*, 210 (1943).

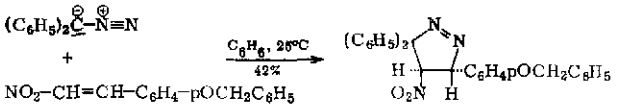
[62] *B. Eistert*, Angew. Chem. *54*, 124 (1941); *W. G. Young, L. J. Andrews, S. L. Lindenbaum*, and *S. J. Cristol*, J. Amer. chem. Soc. *66*, 810 (1944).

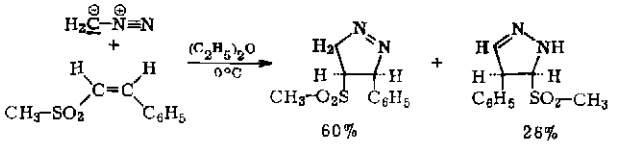
[63] *E. Müller* and *O. Roser*, J. prakt. Chem. (2) *133*, 291 (1932); *K. v. Auwers* and *O. Ungemach*, Ber. dtsch. chem. Ges. *66*, 1198 (1933).

[64] *R. Huisgen, H. Stangl*, and *D. Jung*, unpublished results, München 1960/63.

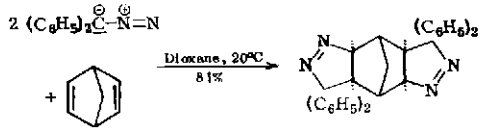
[65] *W. E. Parham, C. Serres*, and *P. R. O'Connor*, J. Amer. chem. Soc. *80*, 588 (1958); *W. E. Parham, H. G. Braxton*, and *P. R. O'Connor*, J. org. Chemistry *26*, 1805 (1961).

[66] *W. E. Parham, F. D. Blake*, and *D. R. Theissen*, J. org. Chemistry *27*, 2415 (1962).



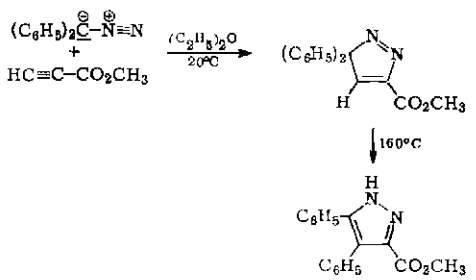


The angularly strained double bond of the bicyclo[2.2.1]-heptene type exhibits a great tendency to accept diazoalkanes. Since bicycloheptadiene gives bis-adducts [67], one may conclude that the second addition step is more rapid than the first.

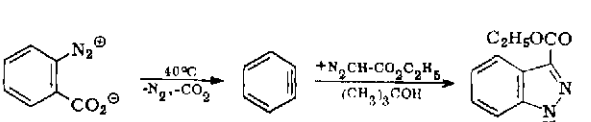


b) *Alkynes as Dipolarophiles*

The sluggish addition of diazomethane onto acetylene to yield pyrazole [68] is in marked contrast to the vigorous reaction with carbonyl-conjugated acetylenes. In ether at 20 °C, dimethyl acetylenedicarboxylate reacts with methyl diazoacetate to give an 85 % yield of trimethyl pyrazole-3,4,5-tricarboxylate [69]. The rates of addition of diphenyldiazomethane to phenylacetylene, methyl propiolate, and diethyl acetylenedicarboxylate in dimethylformamide at 40 °C are in the ratio 1:900:8200 [70]. The addition of diphenyldiazomethane to propiolic ester is followed by aromatization of the primary pyrazolenine either on heating or by acid or alkaline catalysis [71].



Benzyne, a sterically deformed alkyne, is also capable of adding on diazo compounds [72].



[67] *R. Fleischmann*, Ph.D. Thesis, Universität München, 1957.

[68] *H. v. Pechmann*, Ber. dtsch. chem. Ges. *31*, 2950 (1898).

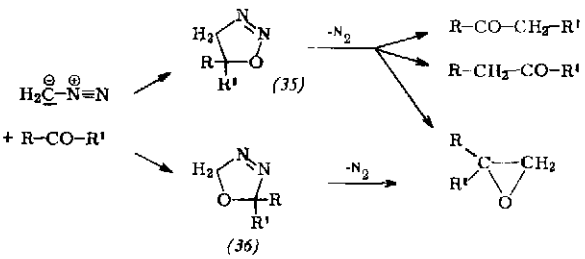
[69] *E. Buchner*, Ber. dtsch. chem. Ges. *22*, 842 (1889).

[70] *R. Huisgen, H. Stangl, H. J. Sturm*, and *H. Wagenhofer*, Angew. Chem. *73*, 170 (1961).

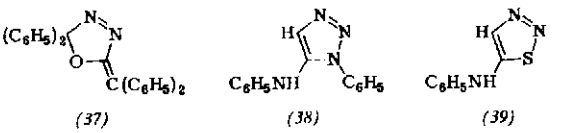
[71] *J. v. Alphen*, Rec. Trav. chim. Pays-Bas *62*, 485 (1943); *R. Hüttel, J. Riedl, H. Martin*, and *K. Franke*, Chem. Ber. *93*, 1425 (1960).

c) *Reactions with Hetero-multiple Bonds*

In 1885, *Th. Curtius* and *E. Buchner* discovered the synthesis of benzoylacetic ester from ethyl diazoacetate and benzaldehyde which has since led to studies of the interaction of diazoalkanes with carbonyl compounds [73]. The most significant results have probably been the ring enlargement of cyclic ketones with diazomethane and the Arndt-Eistert method for increasing the chain length of carboxylic acids. These reactions are interpreted as involving nucleophilic attack of the diazoalkane at the carbonyl carbon, via diazonium and carbonium betaine intermediates [74]. However, a much older interpretation which postulates a 1,2,3-oxadiazoline *(35)* or even a 1,3,4-oxadiazoline *(36)* as an intermediate has never been refuted. The possibility of an initial 1,3-dipolar addition is suggested here. This would not be the first time that a concept believed to be outdated has been revived.



The initial nucleophilic two-center addition is perhaps accomplished only under the influence of electrophilic catalysts [75]. In the presence of aluminum chloride, α,β-unsaturated ketones undergo homologous chain lengthening with diazomethane and addition at the C=C double bond no longer occurs [75]. The formation of the oxadiazoline derivative *(37)* from diphenyldiazomethane and diphenylketene [76] removes all doubt as to an additive interaction with the carbonyl group.



Several additions of diazomethane onto aromatic azomethines, to form Δ²-1,2,3-triazolines, have been described [77]. The addition of diphenylcarbodiimide to yield 33 % *(38)* [78], as well as the reaction of phenyl isothiocyanate with diazomethane to give 60 % of the 1,2,3-thiadiazole derivative *(39)* [79], both follow the same scheme. Here the orientation makes a one-step addition rather improbable.

[72] *R. Huisgen* and *R. Knorr*, Naturwissenschaften *48*, 716 (1961).

[73] Review: *C. D. Gutsche*, Org. Reactions *8*, 364 (1954).

[74] *B. Eistert*, Angew. Chem. *54*, 99 (1941).

[75] *E. Müller* and *M. Bauer*, Liebigs Ann. Chem. *654*, 92 (1962).

[76] *H. Staudinger* and *T. Reber*, Helv. chim. Acta *4*, 3 (1921); *W. Kirmse*, Chem. Ber. *93*, 2357 (1960).

[77] *G. D. Buckley*, J. chem. Soc. (London) *1954*, 1850; *P. K. Kadaba* and *J. O. Edwards*, J. org. Chemistry *26*, 2331 (1961).

[78] *R. Rotter*, Mh. Chem. *47*, 353 (1926).

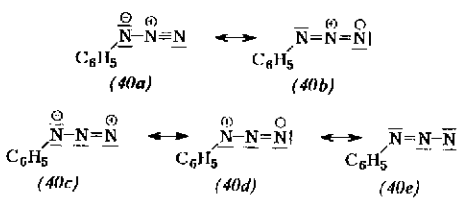
[79] *H. v. Pechmann* and *A. Nold*, Ber. dtsch. chem. Ges. *29*, 2588 (1896); *J. C. Sheehan* and *P. T. Izzo*, J. Amer. chem. Soc. *71*, 4059 (1949).

The normal cyano group does not react with diazomethane. On the other hand, cyanogen, cyanogen halides, and cyanoformic ester give 1,2,3-triazoles [80].

5. Hydrazoic Acid and Azides

The first preparation of an organic azide (*P. Griess*, 1864) occurred almost 100 years ago. The fact that three adjoining nitrogen atoms could yield a stable system was a fascinating phenomenon and is probably responsible for the early development of azide chemistry. In this connection, the Curtius degradation of acyl azides (1890) may be mentioned as an application.

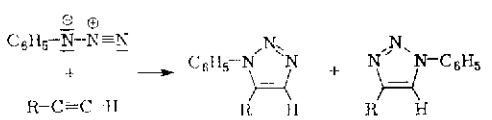
The currently accepted formulation of phenyl azide as a hybrid resonating between the octet formulae *(40a)* and *(40b)* is primarily due to the need for explaining the dipole moment, which amounts to only 1.55 D [81]. Comparison with the value of 0.33 D for *p*-chlorophenyl azide indicates that the azide group withdraws electrons from the benzene nucleus. The x-ray analysis of cyanuric acid triazide [82] indicates that the CN bond is attached to the linear N_3 system at an obtuse angle and that the N–N distances are 1.26 and 1.11 Å. The bond order is to be expected as intermediate between single and double and double and triple bonds, respectively.



(40a) *(40b)* *(40c)* *(40d)* *(40e)*

a) *1,3-Additions to Alkynes*

With the preparation of 1-phenyl-1,2,3-triazole-4,5-dicarboxylic ester from phenyl azide and acetylenedicarboxylic ester, *A. Michael* [83] discovered a simple and valuable synthesis for 1,2,3-triazoles. Alkyl azides and hydrazoic acid are also sufficiently active; acetylene itself and many of its derivatives are suitable dipolarophiles [84]. In additions to monosubstituted acetylenes, the nature of the substituent affects the orientation to a surprisingly small extent. In the case of phenylacetylene [85] or propargylaldehyde acetal [86], the



$R = C_6H_5$	52%	43%
$R = CH(OC_2H_5)_2$	23%	52%

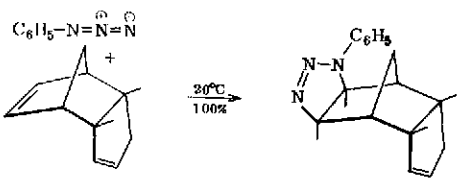
reaction outcome may also be based on the opposing effects of electronic and steric factors.

Benzyne readily adds on aromatic azides to form 1-arylbenzotriazoles [72]. It is remarkable that phenyl azide and its *p*-methoxy derivative give 88 % and 98 % yields, respectively, whereas the electron-poor azide group in *p*-nitrophenyl or tosyl azide fails to undergo reaction.

b) *Alkenes as Dipolarophiles*

1,3-Dipolar addition of azides onto olefinic double bonds is followed more or less readily by evolution of nitrogen from the thermally unstable Δ^2-triazolines which are formed. Since the latter reaction has a higher temperature coefficient, the triazolines are best prepared at as low a temperature as possible, with a reaction time stretching for weeks or months, if need be.

The double bond of bicyclo[2,2,1]heptene has angular strain as shown by its heat of hydrogenation [87] which is some 6 kcal/mole higher than that of cyclohexene. Hence it reacts with especial ease. *K. Alder* and *G. Stein* observed quantitative addition of phenyl azide onto dicyclopentadiene within a few hours [88]. Since bicyclo[2,2,2]octene adds much more slowly, this 1,3-addition served as a test for the demonstration of the energy-rich double bond in bicyclo[2,2,1]heptene derivatives.



An elegant indirect proof that the addition is *exo* is provided by the absence of any influence of massive steric hindrance against *endo* attack in the phenyl azide addition, as well as its complete blocking by substituents on the one-carbon bridge (bornylene) [89]. The adducts of the bicycloheptene series are relatively thermally stable. They lose nitrogen at about 150 °C and give a mixture of aziridines and anils [90]. The intermediate carbonium zwitterion in this process is stabilized by closure of the 3-membered nitrogen-containing ring or by hydride migration. The latter occurs exclusively in the decomposition of the cyclopentene-phenyl azide adduct, which yields the anil of cyclopentanone by loss of nitrogen at about 100 °C.

Treatment with acid causes evolution of nitrogen from Δ^2-triazolines even at room temperature. Any attack on the free pair of electrons of the trigonal nitrogen weakens the triazene mesomerism and favors decomposition. It is therefore understandable that the addition of benz-

[80] *A. Peratoner* and *E. Azzarello*, Gazz. chim. ital. *38*, I, 76 (1908); *E. Oliveri-Mandala*, ibid. *40*, 1, 123 (1910); *C. Pedersen*, Acta chem. scand. *13*, 888 (1959).

[81] *N. V. Sidgwick*, *L. E. Sutton*, and *W. Thomas*, J. chem. Soc. (London) *1933*, 406.

[82] *I. E. Knaggs*, Proc. Roy. Soc. (London), Ser. A *150*, 106 (1937); *E. H. Wiebenga*, J. Amer. chem. Soc. *74*, 6156 (1952).

[83] *A. Michael*, J. prakt. Chem. (2) *48*, 94 (1893).

[84] Reviews: *F. R. Benson* and *W. L. Savell*, Chem. Reviews *46*, 1 (1950); *J. H. Boyer* in *R. C. Elderfield:* Heterocyclic Compounds. Wiley, New York 1961, Vol. 7, p. 387.

[85] *W. Kirmse* and *L. Horner*, Liebigs Ann. Chem. *614*, 1 (1958).

[86] *J. C. Sheehan* and *C. A. Robinson*, J. Amer. chem. Soc. *73*, 1207 (1951).

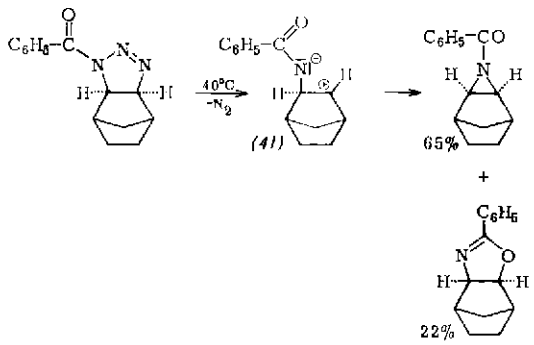
[87] *R. B. Turner*, *W. R. Meador*, and *R. E. Winkler*, J. Amer. chem. Soc. *79*, 4116 (1957); *R. B. Turner* and *W. R. Meador*, ibid. *79*, 4133 (1957).

[88] *K. Alder* and *G. Stein*, Liebigs Ann. Chem. *485*, 211, 223 (1931); *515*, 165 (1935).

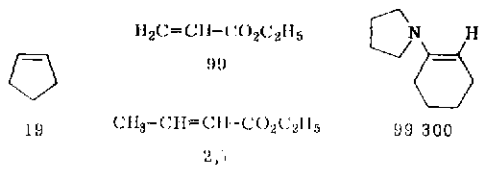
[89] *K. Alder*, *G. Stein*, and *S. Schneider*, Liebigs Ann. Chem. *515*, 185 (1935).

[90] *K. Alder*, *G. Stein*, and *W. Friedrichsen*, Liebigs Ann. Chem. *501*, 1 (1933).

azide to norbornene is followed, even at 40 °C, by loss of nitrogen from the triazoline, leading via *(41)* to the *N*-benzoylaziridine derivative and to an oxazoline structure [91].

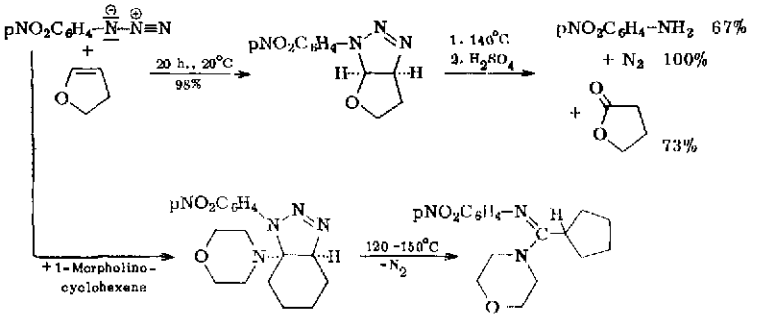


The addition of tosyl azide to a C=C double bond is also followed by rapid evolution of nitrogen from the triazolines with the formation of *N*-tosylimines and *N*-tosylaziridines [91].



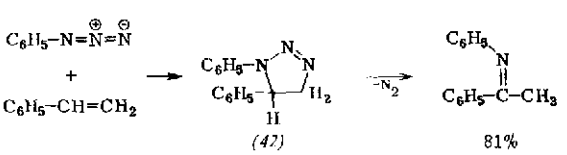
Scheme 1. Rate of addition of phenyl azide onto double bonds. The numbers below the formulae signify 10^8 k_2 [l/mole/sec].

In these 1,3-additions, the outer azide nitrogen, which also is the site of addition of the nucleophilic cyanide ion and of Grignard compounds, always links up with the carbon atom which holds a partial negative charge, *i.e.*, the one in the β-position to the oxygen or nitrogen function. The formation of γ-butyrolactone from the adduct of *p*-nitrophenyl azide and 2,3-dihydrofuran [93] confirms this direction of addition in the case of enol ethers. The ring contraction studied by *R. Fusco* in the azide adducts of 1-morpholinocyclenes indicates the corresponding result for the enamines [94].



The strained double bond of *trans*-cyclooctene also adds phenyl azide exothermically. As the ring size of the *trans*-cycloalkene increases and consequently the angular strain diminishes, the rate of the azide addition decreases rapidly [92].

Conjugation with a phenyl or a carboxylic ester group increases the reactivity of an alkene towards the azide system. In contrast to phenylacetylene, styrene adds phenyl azide in only one orientation. That the product is 1,5-diphenyl-Δ²-triazoline *(42)* is shown by the formation of acetophenone-anil on heating [93].

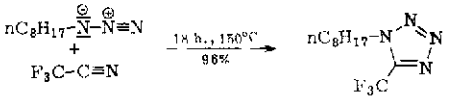


The rapid combination of azides with vinyl ethers and enamines marks a characteristic difference between the azides and the diazoalkanes. Some rates of addition of phenyl azide at 25 °C reveal the superior dipolarophilic activity of the electron-rich double bond [93] (Scheme 1).

c) *Reactions with Hetero-multiple Bonds*

The preparation of tetrazole from hydrogen cyanide and hydrazoic acid requires heating for several days at 100 °C [95]. On the other hand, cyanamide yields 5-aminotetrazole smoothly even at room temperature [96]. Aliphatic nitriles must be heated with HN_3 at 150 °C in order to obtain 5-alkyltetrazoles [97]; it is advantageous to use lithium or ammonium azide in this case [10]. The addition of hydrazoic acid onto imidochlorides offers a useful route to 1,5-disubstituted tetrazoles [98]. It is still not clear whether these are true 1,3-dipolar additions or additions via an imidoyl azide intermediate.

Only the electron-poor C≡N triple bonds of ethyl cyanoformate [93] or of perfluoroalkyl cyanides [99] are capable of adding organic azides (cf. Section B 4c).



[91] *G. Müller*, Ph.D. Thesis, Universität München, 1962.

[92] *K. Ziegler* and *H. Wilms*, Liebigs Ann. Chem. *567*, 1 (1950); *K. Ziegler, H. Sauer, L. Bruns, H. Froitzheim-Kühlhorn*, and *J. Schneider*, ibid. *589*, 122 (1954).

[93] *L. Möbius* and *H. Wagenhofer*, unpublished results, München, 1962.

[94] *R. Fusco, G. Bianchetti*, and *D. Pocar*, Gazz. chim. ital. *91*, 849, 933 (1961).

[95] *O. Dimroth* and *G. Fester*, Ber. dtsch. chem. Ges. *43*, 2219 (1910).

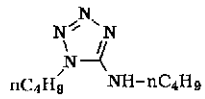
[96] *A. Hantzsch* and *A. Vagt*, Liebigs Ann. Chem, *314*, 339 (1901).

[97] *J. S. Mihina* and *R. M. Herbst*, J. org. Chemistry *15*, 1082 (1950).

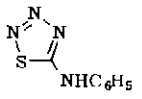
[98] *J. v. Braun* and *W. Rudolph*, Ber. dtsch. chem. Ges. *74*, 264 (1941).

[99] *W. R. Carpenter*, J. org. Chemistry *27*, 2085 (1962).

Additions of azides onto normal C=O or C=N double bonds are not known. However, cumulated systems undergo cycloaddition with HN_3. Dibutylcarbodiimide yields 73 % *(43)* [100], and phenyl isothiocyanate at 100 °C gives 89 % *(44)* [101], while the reaction with carbon disulfide leads to 1,2,3,4-thiatriazoline-5-thione *(45)* [102].



(43)

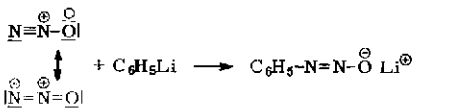


(44)

(45)

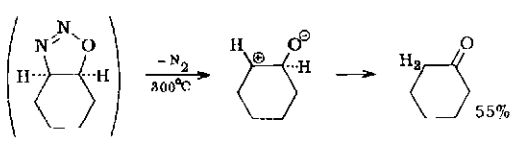
6. Nitrous Oxide

The N_2O molecule was one of the examples used by *L. Pauling* in the thirties in his development of the resonance concept. The bond lengths of 1.13 and 1.19 Å [103], as well as the dipole moment of only 0.17 D [104], indicate nearly equal participation of both octet formulae in the ground state. The nucleophilic and electrophilic properties of nitrous oxide are somewhat limited, *e.g.* Grignard compounds do not react whereas aryl- and alkyl-lithiums do [105].



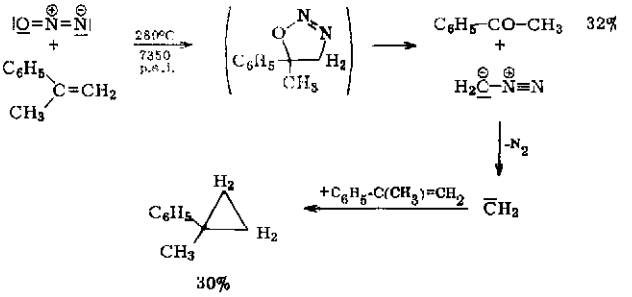
Double and triple CC bonds are perhaps the most suitable coreactants for 1,3-dipolar additions of nitrous oxide, since only here can an appreciable gain in σ bond energy be expected. An English research team carried out some potentially dangerous experiments involving the interaction of N_2O with alkenes and alkynes at 200 to 400 °C and 500 atm pressure [106]. Although these authors isolated neither 1,2,3-oxadiazolines nor 1,2,3-oxadiazoles, they have convincingly explained the formation of the final products isolated on the basis of such cyclic intermediates.

In the reaction of N_2O with cyclohexene at 300 °C, loss of nitrogen from the initial adduct *(46)* is not surprising. Cyclohexanone is produced by a hydride shift within the carbonium zwitterion. With 1-methylcyclohexene, the primary addition of nitrous oxide proceeds in both of the possible directions. The reaction products are 35 % 2-methylcyclohexanone and 30 % cyclopentyl methyl ketone. These result from the hydride shift and a carbonium ion rearrangement, respectively.

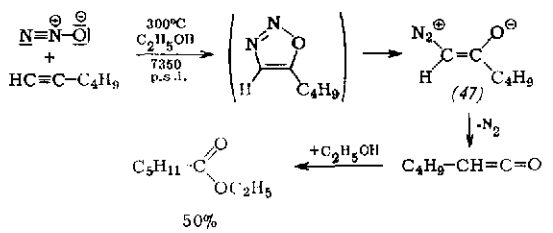


(46)

The reaction of diazoalkanes with carbonyl compounds was also formulated in Section B 4c as proceeding via Δ^2-1,2,3-oxadiazolines or open-chain diazonium zwitterions. Both reactions should thus fall into a common pattern. This appears to be the actual case, and the products isolated from the reaction of α-methylstyrene and N_2O permit the conclusion that the addition of diazoalkanes onto ketones is reversible and that this reverse reaction becomes dominant at 280 °C.



The supposition that the 1,2,3-oxadiazoles expected from alkynes and N_2O react via the open-chain diazoketone is confirmed by the course of reaction observed with 1-hexyne. When the reaction is carried out in ethanol, ethyl caproate is obtained. The intermediate diazoketone *(47)* splits off nitrogen at 300 °C; this is accompanied by a Wolff rearrangement, and the butylketene formed adds ethanol. The analogous reaction in cyclohexylamine even gives 94 % *N*-cyclohexylcaproamide.



C. Additions of 1,3-Dipoles without a Double Bond but with Internal Octet Stabilization

The compounds containing a C=N double bond obtained in reactions of aldehydes or ketones with amines are referred to as Schiff bases, imines, or azomethines. To avoid awkward terminology, the first three members of Table 2 were named azomethine betaines. When our investigations began, only the azomethine oxides (nitrones) were known.

1. Azomethine Ylides

When azomethine ylides are liberated from immonium salts with base, it is necessary to avoid both addition of the base onto the α-carbon atom and abstraction of a β-proton with formation of an enamine. The first azomethine ylide *(48)* was prepared from *N*-(*p*-nitrobenzyl)-3,4-dihydroisoquinolinium bromide with triethylamine in hot pyridine. It is not stable enough to

[100] *D. M. Percival* and *R. M. Herbst*, J. org. Chemistry *22*, 925 (1957).

[101] *E. Lieber, C. N. Pillai*, and *R. D. Hites*, Canad. J. Chem. *35*, 832 (1957).

[102] *E. Lieber, C. N. Pillai, J. Ramachandran*, and *R. D. Hites*, J. org. Chemistry *22*, 1750 (1957).

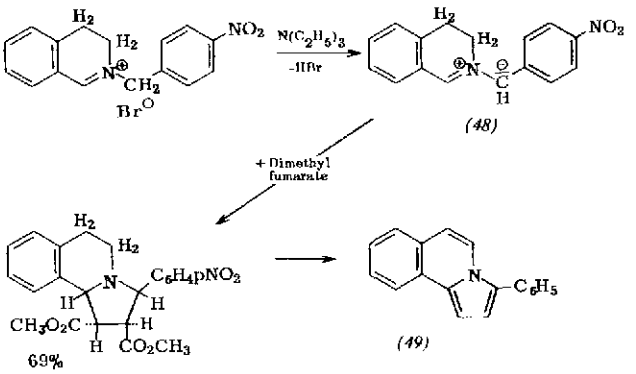
[103] *A. E. Douglas* and *C. K. Moller*, J. chem. Physics *22*, 275 (1954).

[104] *R. G. Shulman, B. P. Dailey*, and *C. H. Townes*, Phys. Rev. *78*, 145 (1950).

[105] *F. M. Beringer, J. A. Farr*, and *S. Sands*, J. Amer. chem. Soc. *75*, 3984 (1953).

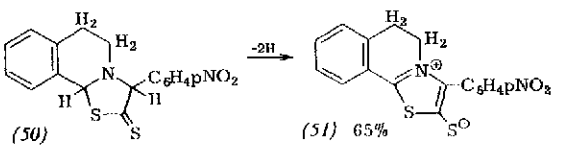
[106] *F. S. Bridson-Jones*, G. D. *Buckley, L. H. Cross*, and A. P. *Driver*, J. chem. Soc. (London) *1951*, 2999; *F. S. Bridson-Jones* and *G. D. Buckley*, ibid. *1951*, 3009; *G. D. Buckley* and *W. J. Levy*, ibid. *1951*, 3016.

be isolated but adds readily to dimethyl fumarate *in situ* [107]. The adduct, isolated in 69 % yield, can be converted via several steps into 3-phenylbenzo-[*g*]pyrrocoline *(49)*. The latter is identical with a preparation obtained by dehydrocyclization of 1-(γ-phenylpropyl)isoquinoline.



(48) *(49)*

Analogous additions of the 1,3-dipole *(48)* onto phenyl isothiocyanate or carbon disulfide are followed by elimination of hydrogen, which is probably transferred to the excess dipolarophile. The hypothetical CS_2 adduct *(50)* leads to the formation of coppery red platelets of the aromatic "sydnone" [107]. In addition to *(51)*, many other resonance forms with various charge distributions can be written.

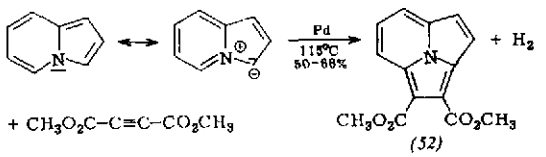


(50) *(51)* 65%

Another short-lived azomethine ylide, which is obtained from *N*-phenacyl-3,4-dihydroisoquinolinium bromide with triethylamine, also undergoes cycloadditions with olefinic dipolarophiles; with *N*-phenylmaleimide in acetonitrile a 73 % yield of the 1:1 adduct is obtained [107]. By the way, these azomethine ylides are the first representatives of the class of compounds christened "nitrenes" by *H. Staudinger* (cf Section C 3a).

With azomethine ylides derived from quaternary salts of the aromatic isoquinoline, even though the C–N double bond is an integral part of the aromatic ring, the ability to undergo addition is retained. The addition of phenyl isothiocyanate onto isoquinoline-*N*-(*p*-nitrobenzylide) is accompanied by loss of two hydrogen atoms, resulting in a 55 % yield of an adduct of the sydnone type [107]. Analogous red betaines are observed on reaction of benzyl- or *p*-substituted benzylisoquinolinium salts with carbon disulfide and alkali [108].

Finally, in this connection the method of *Boekelheide* for the preparation of cyclo[3,2,2]azinedicarboxylic ester from pyrrocoline and dimethyl acetylenedicarboxylate *(52)* in the presence of palladium/charcoal is worthy of mention [109]. Since the reaction does not occur in the absence of palladium, a modest equilibrium concentration of the initially formed 1,3-adduct is evidently stabilized by dehydrogenation.



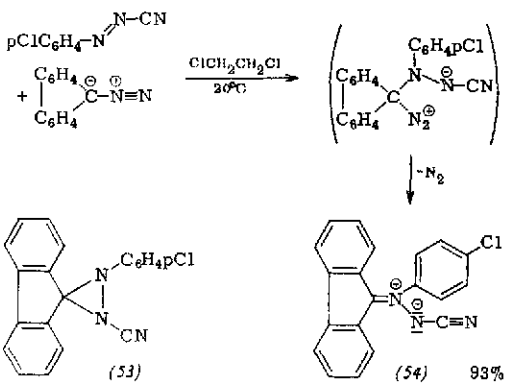
(52)

2. Azomethine Imines

Four years ago, we chose the azomethine imines, a class of compounds that was at that time unknown, as models for the study of 1,3-dipolar cycloadditions in order to test the synthetic scheme and the potentiality of generalizing the reaction. The results were various approaches to the new 1,3-dipole and several hundred successful 1,3-additions. The synthetic routes may be outlined by means of a few examples.

a) *Crystalline N(β)-Cyano(azomethine Imines)*

Aromatic diazocyanides are electrophilic and react with diazoalkanes by evolving one equivalent of nitrogen. Exothermic combination of *p*-chlorobenzenediazocyanide with diazofluorene affords a 93 % yield of the orange-red crystals of *(54)* [110]. Degradation reactions and especially the physical properties demonstrate that this is the open-chain azomethine imine *(54)* and not the isomeric diaziridine *(53)*.



(53) *(54)* 93%

The strong absorption band at 434 mμ agrees with the continuous conjugated system as presented in *(54)*, whereas the chromophoric regions of *(53)* are separated by a tetrahedral center. The unusual long-wave nitrile vibration in the infrared at 4.73 μ, is due to a cyanamide anion; that of sodium phenylcyanamide is found at 4.76 μ. The fluorenyl residue and the cyanamide system provide such good stabilization for the positive and negative charges, respectively, that this azomethine imine makes only minor use of its possibilities for charge cancellation [formulae *(2a)–(2e)*]. The result is an electric moment of 6.62 D (dioxan, 25 °C) in *(54)* (*p*-Br instead of *p*-Cl) [111].

Even though the 1,3-dipole *(54)* is stable to alcohols, it readily participates in cycloadditions with dipolarophiles. Even at 20 °C, dimethyl acetylenedicarboxylate

[107] *R. Huisgen, R. Grashey*, and *E. Steingruber*, Tetrahedron Letters, in the press; *E. Steingruber*, Diploma Thesis, Universität München, 1960.

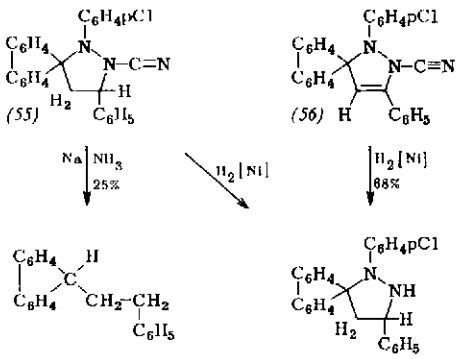
[108] *F. Kröhnke* and *H. Steuernagel*, Angew. Chem. *73*, 26 (1961).

[109] *A. Galbraith, T. Small*, and *V. Boekelheide*, J. org. Chemistry *24*, 582 (1959); cf. *V. Boekelheide* and *A. Miller*, ibid. *26*, 431 (1961).

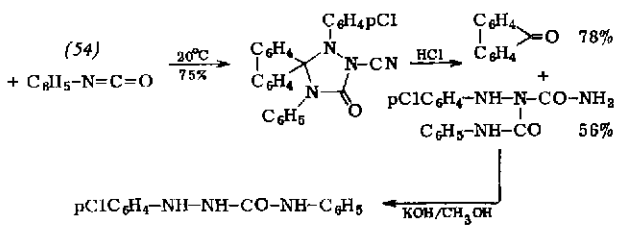
[110] *R. Huisgen, R. Fleischmann*, and *A. Eckell*, Tetrahedron Letters *12*, 1 (1960); *R. Huisgen* and *A. Eckell*, ibid. *12*, 5 (1960).

[111] *A. Eckell*, Ph.D. Thesis, Universität München, 1962.

yields 93 % of a colorless, crystalline 1:1 adduct. The intense absorption of the C=N double bond at 6.33 μ disappears, and the vibration of the nitrile bond then found at 4.49 μ is that of a normal cyanamide. 1,3-Cycloadditions onto styrene, acrylic esters, and norbornene occur at 70–80 °C. 1-Heptene and acetylene, both of which are non-conjugated and therefore react sluggishly, yield adducts to the extent of 85 % in 3 days at 80 °C, and 78 % after 14 days at 48 °C, respectively [110, 111].



The adduct with styrene can be isolated in 92 % yield and reacts with sodium in liquid ammonia. The result is a hydrogenolysis and detachment of the nitrogen function from the benzylic carbon atoms. Degradation to 9-phenethylfluorene indicates the direction in which the styrene addition had occurred. Hydrogenation of *(55)* leads to the tertiary hydrazine with elimination of the cyano residue. This same hydrazine is also obtained by catalytic hydrogenation of the phenylacetylene adduct *(56)*. Thus, the orientations in the additions of both phenylacetylene and styrene are identical [111].

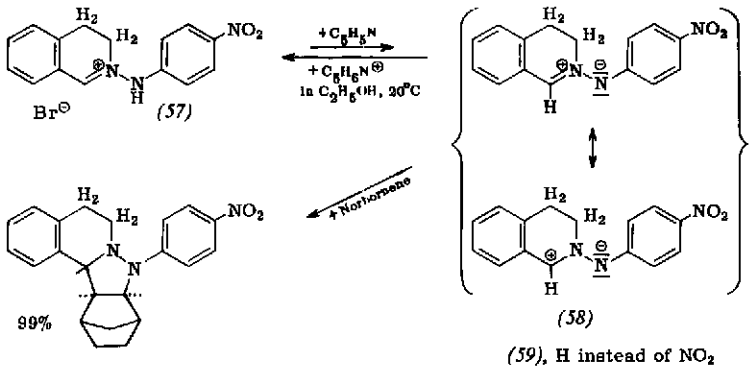


The azomethine imine *(54)* also reacts with the hetero multiple bonds of ethyl cyanoformate, phenyl isocyanate and phenyl isothiocyanate. The elucidation of the structure of the phenyl isocyanate adduct [111] shown in the formulae above requires no comment.

b) *Azomethine Imines of the 3,4-Dihydroisoquinoline Series*

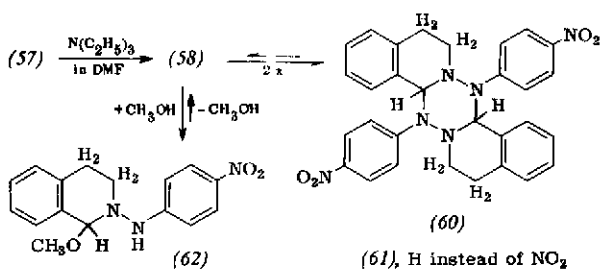
N-Arylamino-3,4-dihydroisoquinolinium salts, which are accessible from 2-(β-bromoethyl)benzaldehyde and arylhydrazines [112, 113], are intramolecular alkylation products of arylaldehyde arylhydrazones. Whereas normally hydrazone alkylation occurs at N(β), the closure of a 6-membered ring here favors N(α)-alkylation. A mere deprotonation with base at the nitrogen suffices to yield a class of highly reactive azomethine imines.

When pyridine is the base, the hydrazonium bromide *(57)* yields a modest equilibrium concentration of the azomethine imine *(58)*. In the presence of norbornene, the latter affords an almost quantitative yield of a crystalline adduct [113]. Treatment of a solution of *(57)* in



(59), H instead of NO_2

dimethylformamide with triethylamine results in a deep red solution of *(58)*. In the absence of a dipolarophile, yellow crystals of the hexahydrotetrazine derivative *(60)* precipitate after a few seconds. The same "head-to-tail" dimerization is also observed with the analogous azomethine imines which have a hydrogen [112], phenyl, *p*-chlorophenyl, benzyl, methyl, *etc.* on the anionic nitrogen [114]. Solutions of *(60)* exhibit reversible thermochromism above 60 °C. This is attributable to dissociation into the monomeric azomethine imine. The same is true of the methanol adduct *(62)*, which, like *(60)*, serves as a stable, convenient, neutral source of the azomethine imine *(58)*. The presence of an $N^{\oplus}$, $N^{\ominus}$-betaine in a hot, red toluene solution of the 2,4-dinitro compound corresponding to *(62)* has already been suggested by *E. Schmitz* [112].



(61), H instead of NO_2

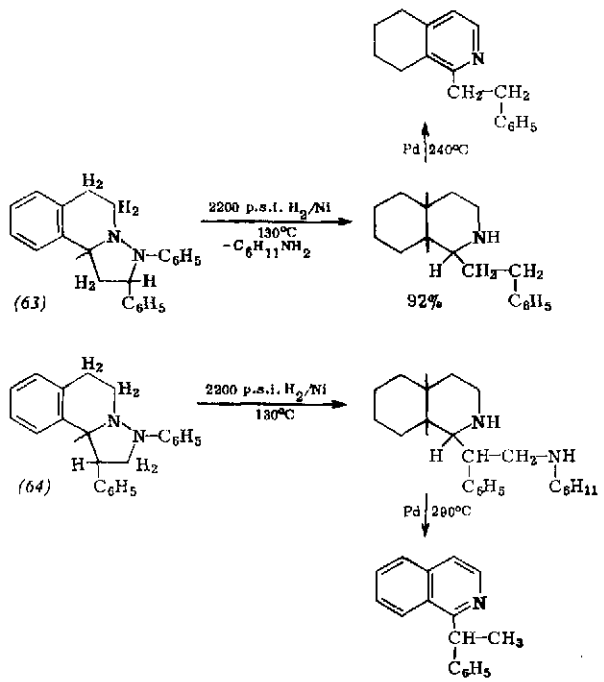
These azomethine imines of the 3,4-dihydroisoquinoline series combine so smoothly with all kinds of alkenes (except for the highly alkylated ones) that they may be recommended as analytical reagents for the identification of liquid olefins, and possibly for the separation of olefin mixtures as well. One disadvantage is that unsymmetrically substituted ethylenes frequently yield structurally isomeric adducts, which differ in their direction of addition. In contrast to *(54)*, the steric relationships (and these determine the orientation to a greater extent than the electronic effects) are so well

[112] *E. Schmitz*, Chem. Ber. *91*, 1495 (1958).

[113] *R. Huisgen, R. Grashey, P. Laur*, and *H. Leitermann*, Angew. Chem. *72*, 416 (1960).

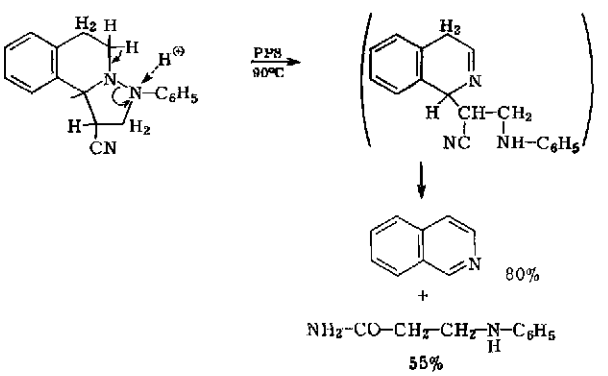
[114] *P. Laur*, Ph.D. Thesis, Universität München, 1962.

balanced in *(58)* that a preferred direction of cycloaddition is virtually undetectable. Thus, ethylene and cyclopentene each yield a single adduct, while allyl alcohol, allylbenzene, styrene, and 1,1-diphenylethylene each yield pairs of isomers. The two adducts obtained from acenaphthylene and *(59)* must be stereoisomeric [113,116].



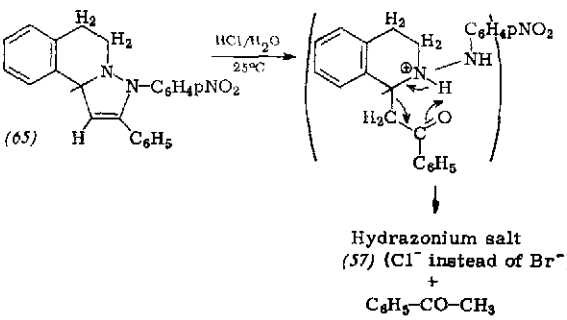
3,4-Dihydroisoquinoline-*N*-phenylimine *(59)* combines with styrene to give 31 % *(63)* and 55 % *(64)*. Hydrogenation of *(63)* under pressure is accompanied by elimination of aniline or cyclohexylamine. Dehydrogenation of the perhydroisoquinoline derivative leads to 1-(β-phenylethyl)-5,6,7,8-tetrahydroisoquinoline, which has been synthetized independently. The hydrogenated base, which is obtained from *(64)* and which still contains two nitrogen atoms, loses cyclohexylamine on aromatization. Here 1-(α-phenylethyl)isoquinoline was identified in the products [114].

C=C Double bonds which are activated by neighboring ketone, carboxylic ester, nitro, or nitrile functions, accept these azomethine imines with special ease, as shown by some yields obtained with *(58)*: acrylonitrile adduct 100 %, maleic anhydride 94 %, ethyl crotonate 85 %, and ethyl *p*-nitrocinnamate 88 %. In experiments where different dipolarophiles compete for *(59)*, methyl

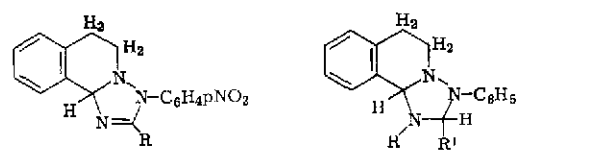


acrylate reacts 1700 times more rapidly than styrene [115]. Dimethyl maleate and fumarate each yield one single (that is, without admixture of the isomer) epimeric pyrazolidine in 95 % and 97 % yields, respectively [113]. The direction of addition may be deduced from cleavage of the adduct of *(59)* and acrylonitrile with polyphosphoric acid [116] as shown below.

Enols, enol ethers, enol esters, and enamines are some of the other reactive alkenes [116]. Alkynes are found to be just as suitable; the lack of isomeric adducts indicates stricter orientation rules. The alkyne adducts are themselves enamines and are therefore acid-sensitive. The hydrolysis is often accompanied by fragmentation, reminiscent of a retro-Mannich reaction. The direction of addition may be deduced from this hydrolysis as has been formulated for the Δ^3-pyrazoline *(65)* obtained from addition of *(62)* to phenylacetylene [116]. The adduct of methyl propiolate, which is isolated quantitatively, however, shows the reverse orientation.



The possibilities for additions to hetero-multiple bonds are quite extensive and varied, but the description will be kept brief here. The methoxylated tetrahydroisoquinoline derivative *(62)* combines with *p*-nitrobenzonitrile to form the Δ^3-1,2,4-triazoline *(66)*, as shown by acid hydrolysis of the product to yield *p*-nitrobenzoic acid and the hydrazonium salt *(57)*. The dipolarophilic activity of the C≡N triple bond in thiocyanates is indicated by a 91 % yield of the benzyl thiocyanate adduct [117].



(66) R = $C_6H_4pNO_2$ 69%
R = $CO_2C_2H_5$ 83%
R = $S-CH_2C_6H_5$ 91%

(67) R = CH_3, R' = C_6H_5 97%
R = $C(CH_3)_3$, R' = H 72%

Cycloaddition of aldehydes onto the 1,3-system leads to derivatives of a hitherto undescribed ring system [118]. As expected, the 1,3,4-oxadiazolidines obtained are readily hydrolysed by dilute acids. The reduction

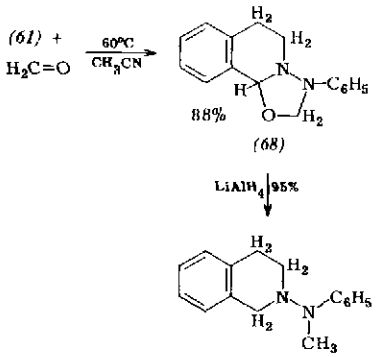
[115] *R. Schiffer*, unpublished results. München.

[116] *R. Grashey*, unpublished results, München.

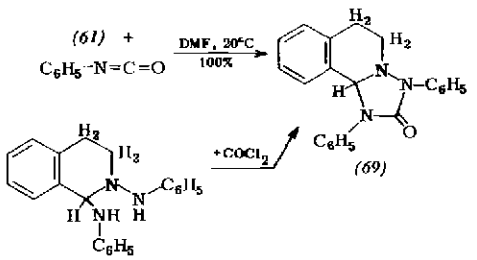
[117] *R. Grashey, H. Leitermann, R. Schmidt*, and *K. Adelsberger*, Angew. Chem. *74*, 491 (1962); Angew. Chem. internat. Edit. *1*, 406 (1962).

[118] *R. Grashey* and *K. Adelsberger*, Angew. Chem. *74*, 292 (1962); Angew. Chem. internat. Edit. *1*, 267 (1962).

with complex hydrides, illustrated for the formaldehyde adduct *(68)*, is also typical of α-aminocarbinols.



Reversible thermochromism occurs above 60 °C and indicates dissociation of the aldehyde adducts into their components. The mobility of this equilibrium is truly astonishing. When the adduct of 3,4-dihydroisoquinoline *N*-phenylimine *(59)* and *p*-nitrobenzaldehyde is heated in the presence of phenyl isocyanate, it yields 94 % of the phenyl isocyanate adduct *(69)* and liberates the aldehyde [118].



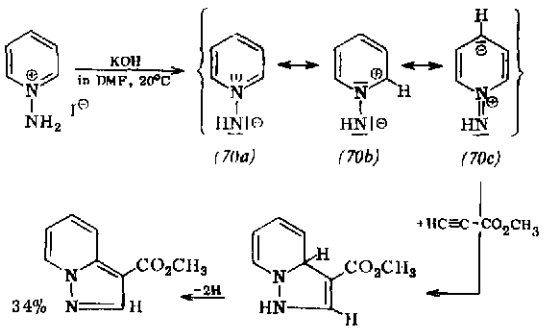
We have thus reached cumulated systems of the isocyanate, isothiocyanate, carbodiimide, and carbon disulfide as dipolarophile types. These are excellent acceptors, for they bind the azomethine imines to form stable adducts in 90–100 % yields. The fact that the reaction between phenyl isocyanate or isothiocyanate and the hexahydrotetrazine derivative *(61)* takes place at 20 °C indicates the possibility of an initial electrophilic attack. Independent synthesis has established that the product has the structure of a 1,2,4-triazolidin-3-one *(69)* [114].

Finally, additions to azomethines yield 1,2,4-triazolidines *(67)*; in this reaction, even the sterically hindered methylene-t-butylamine is still sufficiently dipolarophilic [117]. Here, too, thermal dissociation into the components is encountered, but its thermal instability is lower than that of the 1,3,4-oxadiazolidines.

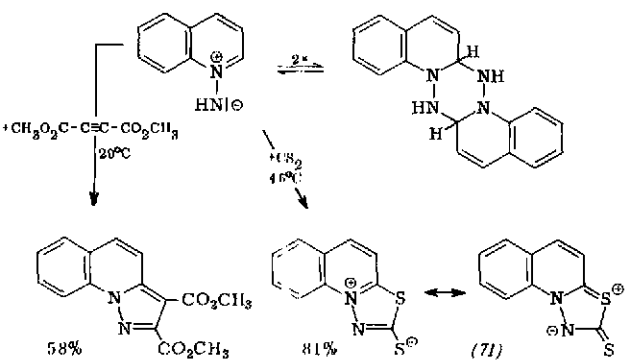
c) *N-Imines of Pyridine, Quinoline, and Isoquinoline*

Experiments with azomethine imines in which the C=N double bond is an integral part of an aromatic ring give convincing proof of the strength of the driving force behind 1,3-dipolar additions. Since this addition involves loss of the aromatic mesomerism, very active dipolarophiles are required.

The *N*-aminopyridinium salt, which is readily obtainable from pyridine and hydroxylamine-*O*-sulfonic acid [119], yields solutions of pyridine-*N*-imine *(70)* when treated with alkali in dimethylformamide. Its reaction with methyl propiolate makes it reasonable to regard this compound as an azomethine imine represented by structures *(70a)* and *(70b)*. The non-aromatic primary adduct is dehydrogenated in the course of the reaction to yield methyl pyrazolo[1,5-*a*]pyridine-3-carboxylate. Degradation to the basic aromatic unit and oxidation to pyrazole-3,4-dicarboxylic acid serve as structure proofs [120].



The *N*-imines of quinoline, isoquinoline, and phenanthridine are prepared analogously and are in dynamic equilibrium with stable dimers, presumably hexahydrotetrazine derivatives. Not only the reaction of *N*-imino quinoline with acetylenedicarboxylic ester, but also that with carbon disulfide is accompanied by loss of hydrogen. In the latter reaction, an 81 % yield of the deep yellow zwitterion *(71)* of the thiazolo[2,3-*a*]quinoline series is obtained [120]. In contrast, addition of dimeric isoquinoline-*N*-imine onto acetylenedicarboxylic ester can be stopped at the stage of the non-aromatic primary adduct.



The deeply colored *N*-arylimines of the aromatic nitrogen bases are more stable than the simple imines, and may sometimes be isolated [121]. Isoquinoline-*N*-arylimines are readily obtainable by dehydrogenation of hydrazonium salts such as *(57)* using nitrosobenzene, followed by treatment with a base [116,122]. Phenyl isocyanate causes rapid decolorization of the red ethereal solution of *(72)*, even at 20 °C. The colorless adduct can be isolated in 87 % yield and exhibits reversible thermochromism; the phenyl isocyanate may be

[119] *R. Gösl* and *A. Meuwsen*, Chem. Ber. *92*, 2521 (1959).

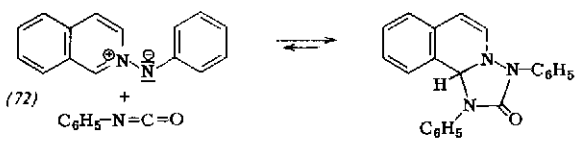
[120] *R. Huisgen, R. Grashey*, and *R. Krischke*, Tetrahedron Letters *1962*, 387.

[121] *W. Schneider*, Liebigs Ann. Chem. *438*, 115 (1924); *W. Schneider* and *K. Weiss*, Ber. dtsch. chem. Ges. *61*, 2445 (1928); *W. Schneider* and *W. Riedel*, ibid. *74*, 1252 (1941).

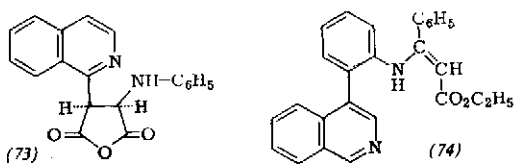
[122] *K. Bast*, Ph.D. Thesis, Universität München, 1962.

trapped in the hot solution. Restoration of the aromatic mesomerism of the nitrogen-containing 6-membered ring undoubtedly contributes to the driving force of the reverse reaction [122].

Although the reactions of *(72)* with phenyl isothiocyanate, acenaphthylene, and 1,4-naphthoquinone yield analogous 1:1 adducts containing 5-membered rings, other 1,3-dipolar additions are followed by rearomatization with ring opening. The adduct of maleic anhydride probably has structure *(73)*. Addition of ethyl phenylpropiolate onto *(72)* at 20 °C is accompanied by a

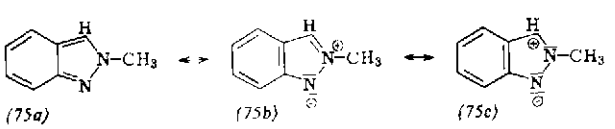


rather unorthodox rearrangement to give *(74)* in 57 % yield [122]. A secondary aromatization is also probable in a compound recently isolated from pyridine-*N*-phenylimine and acrylonitrile [123].

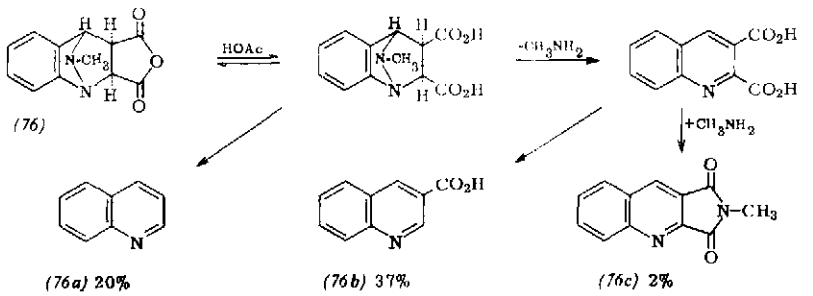


d) *2-Methylindazole*

Another aspect of the problem appears when the entire 1,3-dipole is built into an aromatic ring. 2-Methylindazole *(75)* is undoubtedly aromatic. Even though it can be described only by one neutral structure, its resonance energy is only about 2.4 kcal/mole lower than that of 1-methylindazole [122]. The assumption of a large participation of zwitterionic structures is therefore well justified. The formulae *(75b)* and *(75c)* exhibit the structural elements of an azomethine imine.



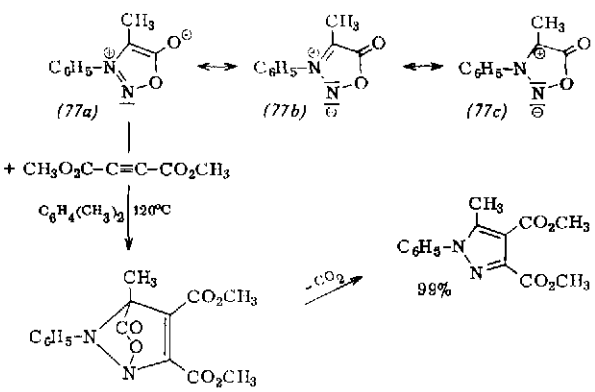
2-Methylindazole reacts with maleic anhydride in glacial acetic acid, whereby the hetero-ring is cleaved. The formation of the three products, *(76a)* through *(76c)*, is readily interpreted as involving initial addition of maleic anhydride onto the 1,3-system to give *(76)*. β-Elimination of methylamine may yield the cyclic methylimide *(76c)* as well as the 3-carboxylic acid *(76b)* by way of quinoline-2,3-dicarboxylic acid. Quinoline itself *(76a)* must be derived from a fragmentation proceeding with loss of the carboxyl group at the 3-position [124].



If the *o*-quinonoid formula *(75a)* of 2-methylindazole is considered, then the formation of *(76)* becomes a Diels-Alder synthesis. In this instance, the distinction between the latter and the 1,3-dipolar cycloaddition is a matter of semantics.

e) *Sydnones*

The problem of mechanistic ambiguity does not exist in the reactive behavior of the sydnones formed from *N*-nitrosoalkyl- or *N*-nitrosoarylaminocarboxylic acids and acetic anhydride. These are aromatic compounds which can be described only by zwitterionic resonance structures, as can be judged from their spectral properties and high dipole moments [125].



Among numerous possible charge distributions, those described by *(77b)* and *(77c)* present the sydnones as azomethine imines. On heating *N*-phenyl-*C*-methylsydnone *(77)* with dimethyl acetylenedicarboxylate for one hour at 120 °C (sydnones start to decompose only at relatively high temperatures), CO_2 is evolved and an almost quantitative yield of dimethyl 1-phenyl-5-methylpyrazole-3,4-dicarboxylate is obtained [126]. In this reaction an initial, rate-determining 1,3-addition is followed by a rapid rearomatization with ejection of carbon dioxide.

[123] *H. Beyer, K. Leverenz*, and *H. Schilling*, Angew. Chem. *73*, 272 (1961).

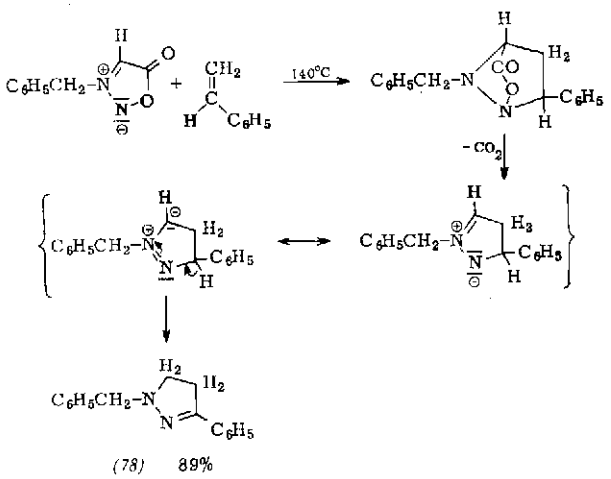
[124] *F. Wimmer*, Ph.D. Thesis, Universität München, 1958.

[125] Review: *W. Baker* and *W. D. Ollis*, Quart. Reviews *11*, 15 (1957).

[126] *R. Huisgen, R. Grashey, H. Gotthardt*, and *R. Schmidt*, Angew. Chem. *74*, 29 (1962); Angew. Chem. internat. Edit. *1*, 48 (1962).

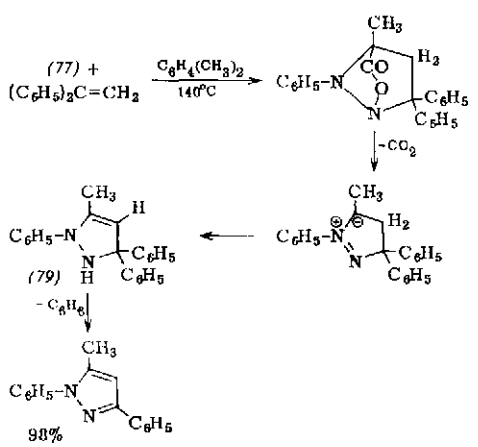
Analogous reactions of sydnones with acetylene, 1-octyne, phenylacetylene, tolane, propargyl alcohol, and phenylbenzoylacetylene show the scope of this fruitful new synthesis of pyrazoles. Occasionally structural isomers occur as products, for example, in the reaction of *N*-phenylsydnone with propiolic ester. The rates of reaction of *(77)* with tolane, phenylacetylene, propiolic ester, and acetylenedicarboxylic ester, measured in terms of CO_2 evolution, are related as 1:13:280:1050 [127]. This emphasizes the accelerating effect of the carboxylic ester function.

A kinetic investigation of the corresponding reaction of alkenes also discloses that the elimination of carbon dioxide occurs after, and not before, the addition of the sydnone onto the C=C double bond. In a formal sense, a new azomethine imine is created with liberation of CO_2 which can then undergo a variety of secondary reactions. The addition of styrene onto *N*-benzylsydnone and decarboxylation are followed by a proton shift to yield 1-benzyl-3-phenyl-Δ^2-pyrazoline *(78)* [128]. Numerous mono- and 1,2-disubstituted ethylenes also form Δ^2-pyrazolines.



(78) 89%

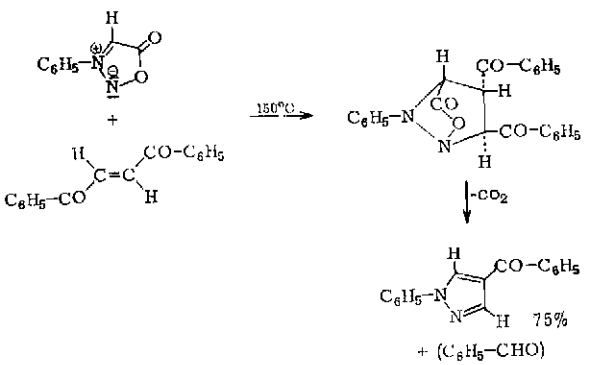
In the case of 1,1-disubstituted ethylenes, no proton is available for the final tautomerization to the Δ^2-pyrazoline. Here, on reaction of α-methylstyrene with *(77)* at 140 °C, CO_2 and methane are evolved to give over 90 % 1,3-diphenyl-5-methylpyrazole. On heating



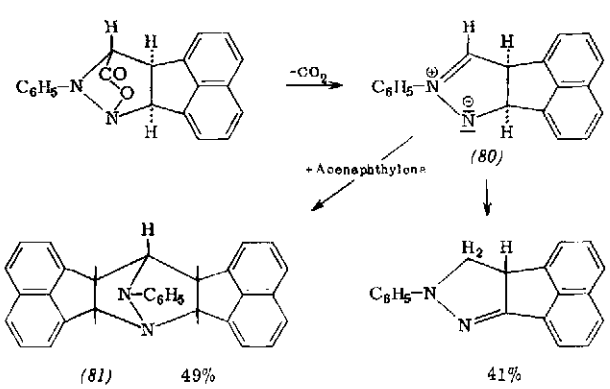
98%

N-phenyl-*C*-methylsydnone *(77)* with 1,1-diphenylethylene in boiling xylene for 24 hours, this same aromatization leads to elimination of benzene – a most surprising phenomenon [128]. Such ejections of alkyl or aryl residues in the course of aromatization at relatively low temperatures are not too common, to say the least. We assume the heretofore unknown Δ^4-pyrazolines, e.g. *(79)*, to be intermediates.

The behavior of *N*-phenylsydnone towards dimethyl fumarate is also unusual. Although the primary adduct is capable of forming a Δ^2-pyrazoline, the product actually isolated in 60 % yield is methyl 1-phenylpyrazole-4-carboxylate, indicating a loss of formic ester and CO_2. The primary adduct of *trans*-dibenzoylethylene undergoes an analogous aromatization [128] as formulated below. The reaction with α,β-unsaturated nitriles yields pyrazoles by elimination of hydrogen cyanide [127, 129]. Additions of sydnones onto *p*-benzoquinone are accompanied by a redox reaction [130]



The azomethine imines resulting from decarboxylation of the primary sydnone adducts should be capable of adding onto a second molecule of alkene via a 1,3-dipolar addition. That the latter reaction would occur with angularly strained double bonds as dipolarophiles appeared probable, since these systems tend to avoid the formation of new sp^2 centers after the first addition. If *N*-phenylsydnone is heated with excess acenaphthylene for 30 minutes at 150 °C, the product isolated consists of 49 % of the 1:2 adduct *(81)* and 41 % of the 1:1 adduct. The 1:1 adduct, which was characterized by its



(81) 49% 41%

[127] *H. Gotthardt*, Ph.D. Thesis, Universität München, 1963.

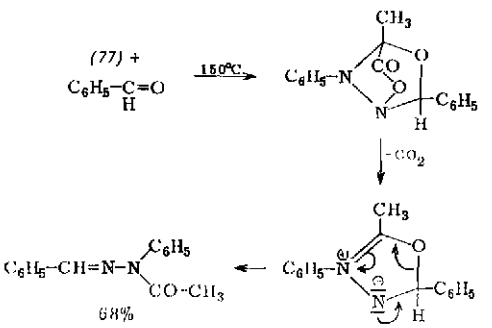
[128] *R. Huisgen, H. Gotthardt, R. Grashey*, and *R. Schmidt*, Angew. Chem. *74*, 30 (1962); Angew. Chem. internat. Edit. *1*, 49 (1962).

[129] *V. F. Vasil'eva, V. G. Yashunskiy, M. N. Shchukina*, Zh. obshch. Khim. *30*, 698 (1960); Chem. Abstr. *54*, 24 674 (1960); Zh. obshch. Khim. *31*, 1501 (1961); Chem. Abstr. *55*, 22291 (1961).

[130] *D. L. Hammick* and *D. J. Voaden*, Chem. and Ind. *1956*, 739.

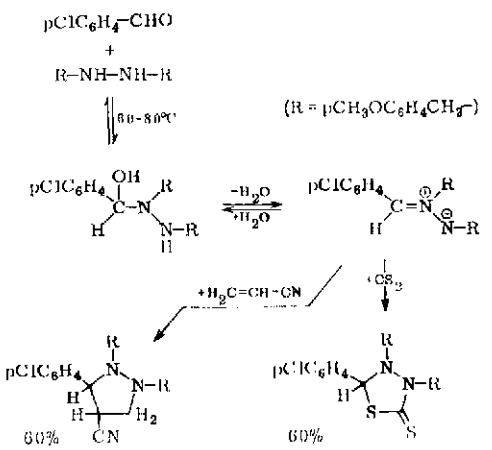
ultraviolet spectrum and fluorescence as a Δ^2-pyrazoline, cannot be converted into the 1:2 adduct with additional acenaphthylene. Thus, the addition of a second molecule of acenaphthylene competes here with the isomerization of the intermediate 1,3-dipole *(80)*. The ultraviolet absorption data agree with formula *(81)* [128].

Finally, mention should be made of the addition of sydnone *(77)* onto the carbonyl group of benzaldehyde. Here the liberation of CO_2 is followed by a cyclic electron shift and ring opening, leading to benzylidene-(α-acetylphenylhydrazine) [127].



f) *1,2-Disubstituted Hydrazines and Carbonyl Compounds*

The interaction of 1,2-disubstituted hydrazines with aldehydes may possibly open a general synthetic route to azomethine imines. At equilibrium, the 1,3-dipole could exist together with the α-hydrazinocarbinol in such a system. However, the characteristic ability of the dipole to undergo addition would be evident even at modest equilibrium concentrations. An example of such a cycloaddition [131] is the reaction of *N,N*-di-(*p*-methoxyphenyl)hydrazine with *p*-chlorobenzaldehyde in acrylonitrile or carbon disulfide. However valuable this synthetic scheme may appear to be, its mechanism has not been established unequivocally.



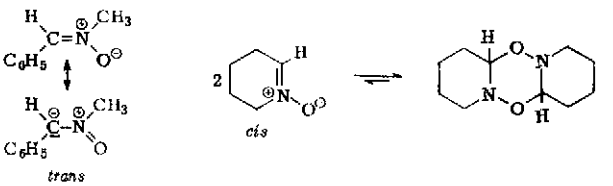
3. Azomethine Oxides (Nitrones)

While alkylating oximes in the 1880's, *E. Beckmann* was the first to obtain azomethine-*N*-oxides as by-products of the *O*-ethers. Besides oxidation of secondary hydroxylamines, the reaction of carbonyl compounds with monosubstituted hydroxylamines is probably the most practical route leading to this class of compounds. The designation "nitrones" was arrived at by analogy to "ketones" [132] and appears to be the result of a misinterpretation.

[131] *R. Grashey, R. M. Moriarty,* and *K. K. Sun,* unpublished results, München, 1960/63.

[132] *P. Pfeiffer,* Liebigs Ann. Chem. *411*, 72 (1916).

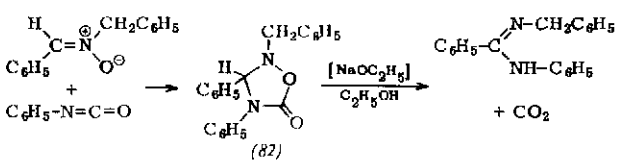
The open-chain structure proposed as early as 1889 [133] was confirmed later by physical measurements and to even a greater extent by isolation of geometrically isomeric nitrones [134]. Dipole moments and ultraviolet spectra [135] served to assign the configurations. Aldonitrones prefer *trans*-orientation of the organic residue relative to the C=N double bond. In Δ^1-piperideine-*N*-oxide, the *cis*-form is dictated by the ring structure; in contrast to the normal nitrones, this compound is a dimer [136]. Even though the dipole moments (*e.g.* 3.55 D for *C*-phenyl-*N*-methylnitrone) indicate that the oxide-type-resonance formula is preferred in the ground state, the second, all-octet structure also makes a significant contribution.



The hydrolysis of nitrones, as well as their reactions with hydrogen cyanide, arylhydrazines, Grignard reagents, complex hydrides, and catalytically activated hydrogen, indicate primary 1,3-additions. In view of the extensive literature on nitrones it is surprising that prior to our work only a single kind of cycloaddition had been observed, namely that onto the C=N double bond of phenyl isocyanate.

a) *Reactions with Isocyanates, Isothiocyanates, and Ketenes*

The reaction of phenyl isocyanate with "*N*-benzyl-β-benzaldoxime" was studied in 1890 [137] in connection with investigations of oxime isomerism. *Beckman* described this compound in terms of formula *(82)*, *i.e.* as a derivative of 1,2,4-oxadiazolidin-5-one. This conclusion was based mainly on the results of a cleavage reaction catalysed by sodium alkoxide.



A later interpretation [138], according to which the adduct contains a 4-membered ring, is less convincing; nevertheless, the structure proposed by *Beckmann* requires further confirmation. The exothermic reactions of *C,N*-diphenylnitrone, *C*-phenyl-*N*-methylnitrone, and 3,4-dihydroisoquinoline-*N*-oxide with phenyl isocyanate yield, respectively, 81 %, 94 %, and 96 % of the crystal-

[133] *K. v. Auwers* and *V. Meyer,* Ber. dtsch. chem. Ges. *22*, 705 (1889).

[134] *L. Semper* and *L. Lichtenstadt,* Ber. dtsch. chem. Ges. *51*, 928 (1918).

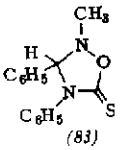
[135] *L. E. Sutton* and *T. W. J. Taylor,* J. chem. Soc. (London) *1931*, 2190; *J. Thesing* and *W. Sirrenberg,* Chem. Ber. *91*, 1978 (1958).

[136] *J. Thesing* and *H. Mayer,* Chem. Ber. *89*, 2159 (1956); Liebigs Ann. Chem. *609*, 46 (1957).

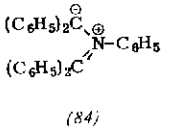
[137] *E. Beckmann,* Ber. dtsch. chem. Ges. *23*, 1680, 3331 (1890); *27*, 1957 (1894); *H. Goldschmidt,* ibid. *23*, 2746 (1890).

[138] *H. Staudinger* and *K. Miescher,* Helv. chim. Acta *2*, 554 (1919).

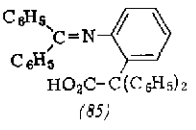
line adducts [116]. A 1:1 adduct obtained from *C*-phenyl-*N*-methylnitrone and phenyl isothiocyanate is presumably 2-methyl-3,4-diphenyl-1,2,4-oxadiazolidine-5-thione *(83)* [116].



(83)



(84)



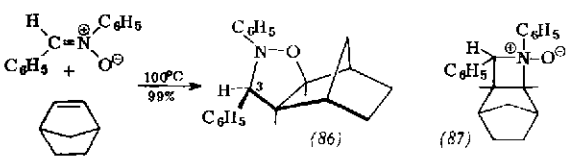
(85)

According to *Staudinger* and *Miescher* [138], a cycloaddition to the "N=O double bond" of the *N*-arylnitrones is responsible for the products obtained with diphenylketene. The products of decarboxylation of the alleged β-lactones were referred to as "nitrenes" *e.g. (84)* which was thought to result from triphenylnitrone and diphenylketene. Only much later was it recognized that the *N*-aryl residue is involved in the reaction, and that the adduct is actually the carboxylic acid *(85)* [139].

b) *1,3-Additions to Alkenes*

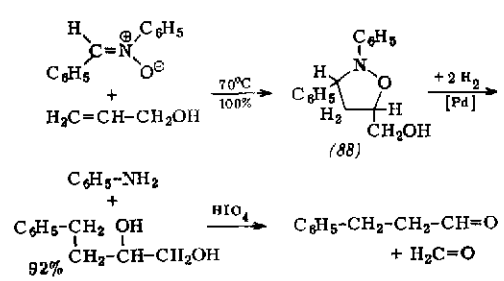
Additions of nitrones onto C=C double bonds proceed in excellent yield and open a convenient route to isoxazolidines. This cycloaddition was discovered only in recent years by several groups, working independently.

The angularly strained double bond of norbornene reacts with *C,N*-diphenylnitrone almost completely at 100 °C; the two crystalline isomers *(86)*, obtained in nearly equal quantities, are presumably epimeric at the 3-position [140]. Cleavage of the isoxazolidine ring with hydrogen and Raney nickel proceeds readily and leads to the β-amino alcohol. The course of this hydrogenation excludes the possibility of an adduct with formula *(87)*, containing a 4-membered ring.



(86) *(87)*

Because of the absence of side reactions, additions of nitrones onto ordinary, non-conjugated olefins also proceed quite smoothly. Thus, *C*-phenyl-*N*-methylnitrone yields adducts with 1-heptene, cyclopentene, and safrol in 92, 90, and 97 % yield, respectively [141]. The direction of addition is determined by means of hydrogenolysis, as shown for product *(88)*, which is obtained



(88)

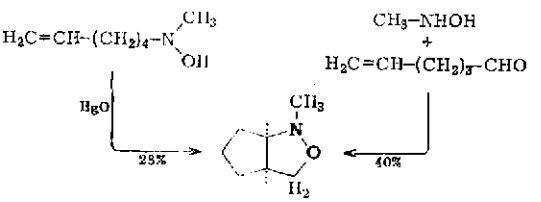
[139] *C. H. Hassall* and *A. F. Lippmann*, J. chem. Soc. (London) *1953*, 1059.

[140] *G. Wallbillich*, Diploma Thesis, Universität München, 1959.

[141] *R. Grashey*, *R. Huisgen*, and *H. Leitermann*, Tetrahedron Letters *12*, 9 (1960).

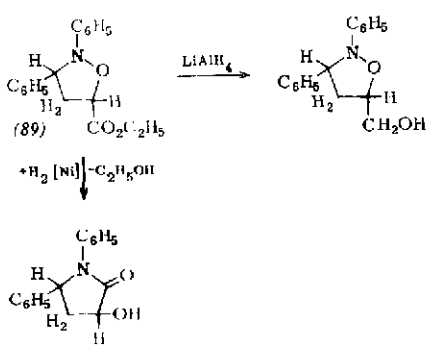
from *C,N*-diphenylnitrone and allyl alcohol. In the presence of palladium, hydrogen not only opens the N-O bond, but also hydrogenolyses the benzyl-*N*-bond [141].

Oxidation of *N*-methyl-*N*-Δ⁵-hexenylhydroxylamine with mercuric oxide causes an intramolecular cycloaddition of the nitrone group onto the C=C double bond. Reaction of *N*-methylhydroxylamine with Δ⁵-hexenal gives the same product [142].



The addition of cyclic nitrones onto 1,3-dienes has been investigated by *Rogers* et al. [143]; these workers were probably the first to prepare isoxazolidines by this route. Thus, 62 % of a 1:1 adduct was obtained from piperideine-*N*-oxide and cyclopentadiene. Styrene and α-methylstyrene combine with *C,N*-diphenylnitrone at 85 °C to give pairs of epimeric adducts in 100 % and 71 % yield, respectively. The structure of the corresponding identical hydrogenolysis products shows that the phenyl residue of the styrene appears exclusively at the 5-position of the isoxazolidine ring [116, 144].

The highly reactive double bond of acrylic ester reacts with *C,N*-diphenylnitrone at 75 °C to form the adduct with 97 % yield, the orientation being the same as in all other monosubstituted ethylenes. Hydrogenation of the adduct *(89)* with lithium aluminum hydride gives the allyl alcohol adduct, while that with catalytically activated hydrogen is accompanied by a ring closure to give a γ-lactam [144]. The same direction of addition has been determined for the adduct obtained from 5,5-dimethyl-Δ¹-pyrroline-*N*-oxide and acrylic ester [145].



(89)

It is not even necessary to use isolated, pure nitrones. The preparation of many aliphatic nitrones in a pure state is in fact not feasible or is accomplished only

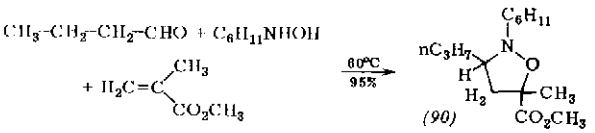
[142] *N. A. LeBel* and *J. J. Whang*, J. Amer. chem. Soc. *81*, 6334 (1959); *N. A. LeBel*, *G. M. J. Slusarczuk*, and *L. A. Spurlock*, ibid. *84*, 4360 (1962).

[143] *C. W. Brown*, *K. Marsden*, *M. A. T. Rogers*, *C. M. B. Tylor*, and *R. Wright*, Proc. chem. Soc. (London) *1960*, 254.

[144] *H. Hauck*, Diploma Thesis, Universität München, 1961, and unpublished results.

[145] *G. R. Delpierre* and *M. Lamchen*, Proc. chem. Soc. (London) *1960*, 386.

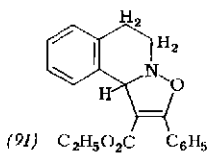
with large losses. If *N*-cyclohexylhydroxylamine and butyraldehyde are combined in methyl methacrylate as the solvent, then *C*-propyl-*N*-cyclohexylnitrone adds *in situ* to the excess alkene to give *(90)* [116,141].



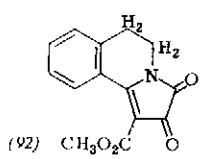
C-Acylnitrones are especially reactive; *C*-benzoyl-*N*-phenylnitrone adds 110 times faster onto ethyl crotonate (toluene, 100 °C) than does *C*,*N*-diphenylnitrone [146]. The isatogens also contain a cyclic *N*-acylnitrone structure and have recently been shown to undergo cycloadditions. Thus 2-phenylisatogen reacts at 20 °C with acrylonitrile, nitroethylene [147], styrene, norbornene, cyclopentene, vinyl ethers, *etc.* [144].

c) *Reactions with Alkynes*

Acetylenes react faster with nitrones than do the analogously substituted ethylenes, but the adducts obtained readily undergo further reactions. In the reaction of 3,4-dihydroisoquinoline-*N*-oxide with phenylpropiolic ester, 69 % of a colorless primary adduct *(91)* can be obtained. On the other hand, addition of dimethyl acetylenedicarboxylate onto the same cyclic nitrone is followed by an interesting ring opening of the Δ^4-isoxazoline; lactamization then occurs yielding a red product that has been shown to be the pyrrolinedione *(92)* [146].



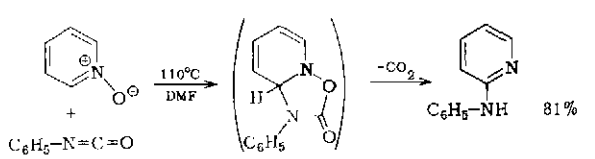
(91)



(92)

d) *Heteroaromatic N-Oxides as 1,3-Dipoles*

Just as pyridine-*N*-imines were treated as 1,3-dipoles in Section C 2c, pyridine-*N*-oxide may also be regarded as a nitrone with a C–N double bond that is incorporated into an aromatic ring. The reaction with phenyl isocyanate has been studied independently in a Japanese laboratory and at Munich [146,148]. The intermediate was not isolated, but it can be guessed that it is analogous to *Beckmann*'s nitrone adduct *(82)*. 2-(Phenylamino)pyridine was formed with loss of carbon dioxide. The *N*-oxides of isoquinoline and phenanthridine react analogously. Isoquinoline-*N*-oxide combines with phenyl isothiocyanate at 70 °C with loss of carbonyl sulfide and yields 61 % of 1-phenylaminoisoquinoline [146].

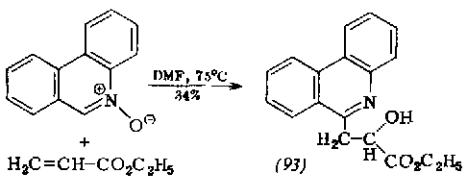


[146] *H. Seidl*, Diploma Thesis, Universität München, 1961, and unpublished results.

[147] *W. E. Noland* and *D. A. Jones*, Chem. and Ind. *1962*, 363.

[148] *E. Hayashi*, J. pharmac. Soc. Japan *81*, 1030 (1961).

Addition to carboxylic esters of the ethylene and acetylene series also occurs readily. The product *(93)* obtained from the reaction of phenanthridine-*N*-oxide and acrylic ester indicates an additional opening of the isoxazolidine ring during the course of rearomatization. After elimination of water by means of acetic anhydride, oxidation affords phenanthridine-6-carboxylic acid. Propiolic and acetylenedicarboxylic esters react exothermically with isoquinoline-*N*-oxide even at room temperature; the structure of the adducts has been elucidated [146].



(93)

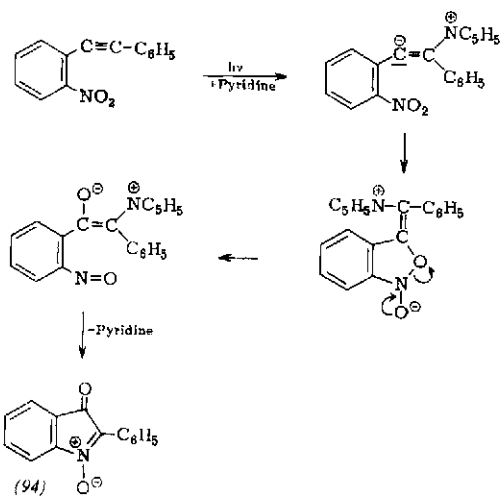
4. Nitro Compounds

Since the nitro group is exceptionally well stabilized by resonance, its tendency to undergo cycloadditions should be very small. If such a reaction were to exist, the intramolecular type of addition should be favored for entropy reasons. The extent to which cycloadditions account for the numerous redox reactions between aromatic nitro groups and *ortho* side-chains remains to be determined.

a) *Interaction with Neighboring Carbon Functions*

In 1881, *A. von Baeyer* discovered the conversion of *o*-nitrophenylpropiolic ester into the so-called isatogenic ester [149]. This reaction may be executed with either cold concentrated sulfuric acid or hot pyridine [150].

The photochemical formation of isatogen *(94)* from *o*-nitrotolane or, even more readily, from *o*-nitro-α-chlorostilbene or *o*-nitrostilbene dichloride, is limited to reactions occurring in pyridine or similar basic solvents [150]. Bredt's rule forbids intramolecular cycloaddition of the nitro group onto the C≡C triple bond.

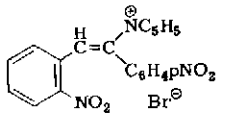


(94)

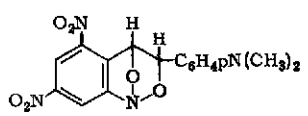
[149] *A. v. Baeyer*, Ber. dtsch. chem. Ges. *14*, 1741 (1881).

[150] *P. Pfeiffer*, Ber. dtsch. chem. Ges. *45*, 1819 (1912); *P. Pfeiffer*, *S. Braude*, *R. Fritsch*, *W. Halberstadt*, *G. Kirchhoff*, *J. Kleber*, and *P. Wittkop*, Liebigs Ann. Chem. *411*, 72 (1916).

The catalysis by pyridine makes another mechanism more likely in which only one oxygen of the nitro group is involved in the cyclic interaction. A nitroso compound can be detected as intermediate. The spontaneous formation of an isatogen from the pyridinium salt *(95)* in the presence of sodium carbonate [151] leads to the supposition that only the first step, namely the formation of the pyridinium betaine, is of a photochemical nature.



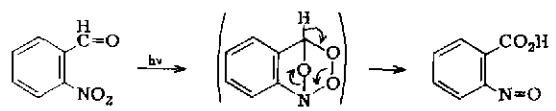
(95)



(96)

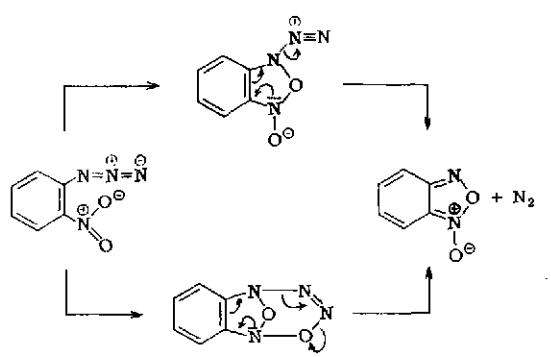
Splitter and *Calvin* observed a photochemical synthesis of isatogen from certain *o*-nitrostilbene derivatives [152] which was accompanied by redox reactions. A spectrum measured during the reaction of 2,4,6-trinitro-4'-dimethylaminostilbene showed an intermediate to which *Splitter* and *Calvin* tentatively assigned structure *(96)*, which could result from a 1,3-dipolar addition. This mechanistic deduction is, however, hardly a proof since even a two-center reaction permits the oxygen shift, as shown above.

Ciamician and *Silber* described the photolytic rearrangement of *o*-nitrobenzaldehyde to *o*-nitrosobenzoic acid [153]. *o*-Nitrobenzalaniline undergoes a corresponding photoisomerization to *o*-nitrobenzanilide [154]. An intramolecular concerted addition is possible in this case, but not obligatory.

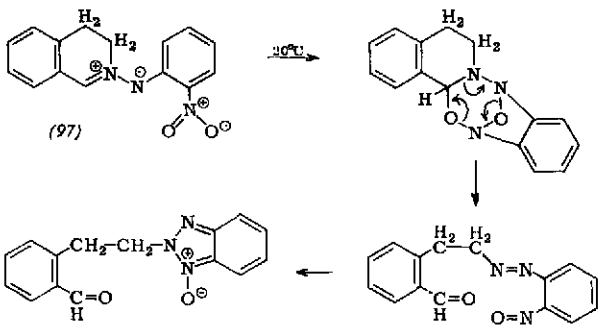


b) *Reactions with ortho Side Chains Containing Nitrogen*

On gentle heating, *o*-nitrophenyl azide decomposes with elimination of nitrogen and formation of benzofuroxan [155]. The decomposition temperature lies considerably below that of phenyl azide, which suggests initial interaction of the nitro group with the azide system. Either a two-center or a four-center process appears feasible.



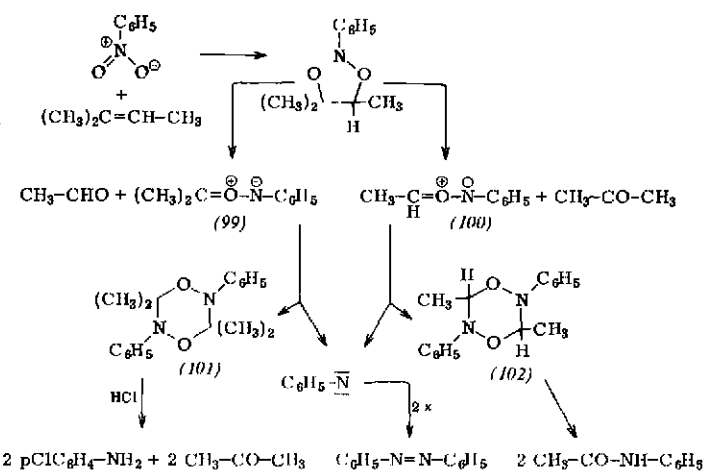
An intramolecular stabilization of 3,4-dihydroisoquinoline-*N*-(*o*-nitrophenyl)imine seems fascinating and is possibly based on a cycloaddition according to a 3 + 3 scheme. Although *(97)* does add, for example, to phenyl isocyanate in the usual way, dimerization of the 1,3-dipole as described in Section C 2b fails to occur. Instead, isomerization takes place to give 89 % of a compound which contains a carboxaldehyde group instead of the nitro group. The assumption of possible intramolecular interaction, as outlined below, suggested structure *(98)*, which was confirmed by an independent synthesis [156]. A cyclic electron shift in the primary adduct generates a formyl, a nitroso, and an azo group. The subsequent reaction of the latter two functions follows known patterns.



(97) *(98)* 89%

c) *Photoreaction of Nitrobenzene with Trimethylethylene*

Büchi and *Ayer* attempted to explain the rather complicated course of this reaction by assuming an initial 1,3-addition to give a 1,3,2-dioxazolidine derivative [157]. Acetanilide, azobenzene, and a compound said be *(101)* were isolated in addition to 12 % acetaldehyde plus acetone.



(99) *(100)* *(101)* *(102)*

The authors suggest decomposition of the cyclic adduct into acetaldehyde or acetone and the carbonylimines *(99)* or *(100)*. Thus, we would be dealing here with the first representatives of this class of 1,3-dipoles (listed in Table 2). Along with the "head-to-tail" dimerization to give *(101)* and *(102)*, a further decomposition to a carbonyl compound and

[151] *F. Kröhnke* and *M. Meyer-Delius*, Chem. Ber. *84*, 932 (1951).

[152] *J. S. Splitter* and *M. Calvin*, J. org. Chemistry *20*, 1086 (1955).

[153] *G. Ciamician* and *P. Silber*, Ber. dtsch. chem. Ges. *34*, 2040 (1901).

[154] *F. Sachs* and *R. Kempf*, Ber. dtsch. chem. Ges. *35*, 2704 (1902).

[155] *E. Noelting* and *K. Kohn*, Chem. Ztg. *18*, 1095 (1894); *Th. Zincke*, J. prakt. Chem. (2) *53*, 340 (1896).

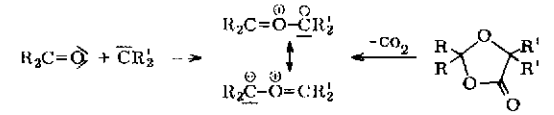
[156] *R. Grashey*, Angew. Chem. *74*, 155 (1962); Angew. Chem. internat. Edit. *1*, 158 (1962).

[157] *G. Büchi* and *D. E. Ayer*, J. Amer. chem. Soc. *78*, 689 (1956).

phenylazene is also assumed to occur. Compounds *(101)* and *(102)* should dissociate spontaneously into nitrones (cf. Section C3, introduction); the final products are also consistent with their occurrence.

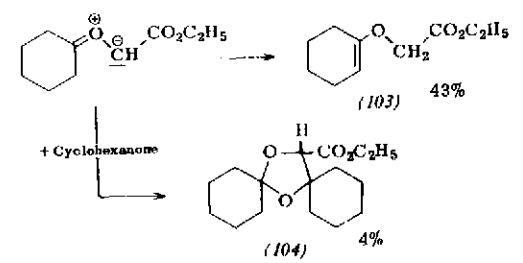
5. Carbonyl Ylides

The addition of a carbene onto the oxygen of a carbonyl group is, in a formal sense, the simplest and the easiest route to these 1,3-dipoles. Our attempts to obtain this system by thermolysis of 1,3-dioxolan-4-ones did not yield clear-cut results [158]. So far no carbonyl ylide has proved sufficiently stable to permit its isolation, but their occurrence as intermediates is plausible.



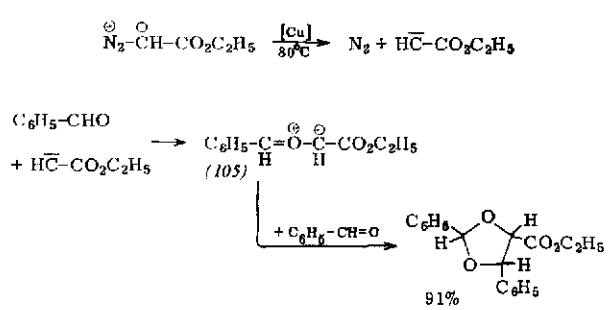
a) *Reactions of Carbonyl Compounds with Carbenes*

M. S. Kharasch et al. decomposed ethyl diazoacetate in cyclohexanone to form the enol ether *(103)* and two 2:1 adducts of cyclohexanone and ethoxycarbonylcarbene [159]. The carbonyl ylide postulated as an intermediate either undergoes a proton shift to form *(103)* or takes up a second molecule of ketone in a 1,3-dipolar addition to give *(104)*. Copper-catalysed decomposition of diazoacetic ester in boiling acetone gives 9% of a compound corresponding to *(104)*.



(103) *(104)*

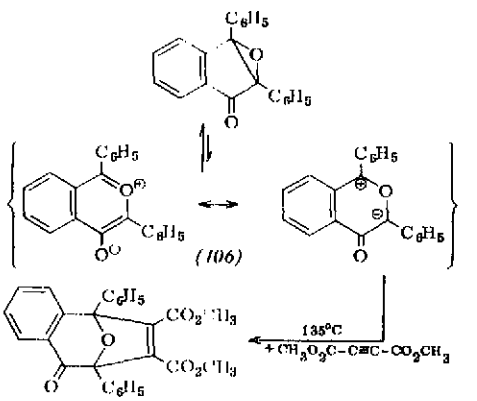
By the fact that no nitrogen is evolved on heating ethyl diazoacetate at 80 °C in excess benzaldehyde, the absence of any interaction of the components at this temperature is indicated. If the decomposition of the diazoacetic ester is now induced by copper catalysis, a 91% yield of two diastereomeric dioxolans is achieved [158]. The ethoxycarbonylcarbene combines with the carbonyl oxygen to form the carbonyl ylide *(105)* which, as a 1,3-dipole, adds a second molecule of benzaldehyde. The same dioxolanes are obtained on thermolysis at 160–170 °C [160], but the course of this reaction is not clearly defined.



The corresponding reaction of benzophenone with ethoxycarbonylcarbene yields the 2:1 adduct to only a minor extent; possibly for steric reasons, ring closure of the 1,3-dipole predominates and gives ethyl diphenylglycidate. On the other hand, the copper-catalysed reaction of diazomalonic ester in benzaldehyde proceeds smoothly and forms diethyl 2,4-diphenyl-1,3-dioxolane-5,5-dicarboxylate [158].

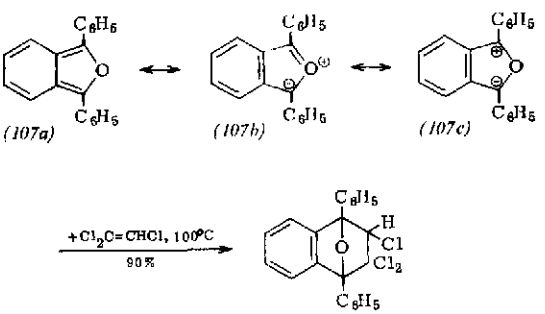
b) *Pyrylium Oxides*

The reversible thermochromism of 2,3-diphenylindenone-2,3-epoxide has been recently attributed by *Ullman* and *Milks* to a pyrylium zwitterion *(106)* [161]. The ability of the latter to add on norbornadiene or dimethyl acetylenedicarboxylate to form 5-membered rings is convincing evidence that it is correct to regard the pyrylium oxide as a 1,3-dipole.



c) *1,3-Diphenylisobenzofuran*

Cycloadditions of 1,3-diphenylisobenzofuran *(107)* were discovered by *Weiss* and were considered at that time to be Diels-Alder reactions [162]. Along with the *o*-quinonoid resonance formula *(107a)*, in which the molecule appears as a 1,3-diene, the ground state undoubtedly also involves participation of zwitterionic structures such as *(107b)* and *(107c)*. When these two formulae are considered, a carbonyl ylide can readily be recognized in the isobenzofuran structure. Here, just as with 2-methylindazole (Section C 2d), distinction between diene synthesis and 1,3-dipolar addition becomes meaningless.



[158] *R. Bermes*, Diploma Thesis, Universität München, 1961.

[159] *M. S. Kharasch, T. Rudy, W. Nudenberg*, and *G. Büchi*, J. org. Chemistry *18*, 1030 (1953).

[160] *W. Dieckmann*, Ber. dtsch. chem. Ges. *43*, 1024 (1910).

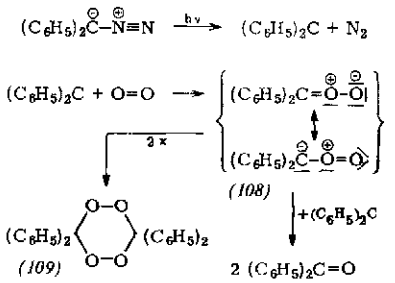
[161] *E. F. Ullman* and *J. E. Milks*, J. Amer. chem. Soc. *84*, 1315 (1962).

It is noteworthy that the list of reagents capable of undergoing 1,3-additions with 1,3-diphenylisobenzofuran is not limited to normal dienophiles such as maleic anhydride, quinones, and acrylic esters, but also includes indene [162], styrene [158], and trichloroethylene [158]. Electron-rich double bonds, such as those in 2,3-dihydropyran or vinyl acetate, also react with *(107)* [158]. The great ease with which *(107)* undergoes addition at angularly strained double bonds can be deduced from its tendency to form a 2:1 adduct with propiolic ester. Because of its high reactivity, 1,3-diphenylisobenzofuran is useful for trapping benzyne [163], highly strained cycloalkynes [164], or benzocyclobutadiene [165].

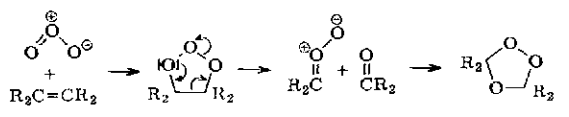
6. Carbonyl Oxides

a) *Synthetic Routes*

Carbonyl oxides should be obtainable by addition of an oxygen atom to the carbonyl oxygen or by addition of a carbene onto the oxygen molecule. Only the latter method has so far been reported. On photolysis of diphenyldiazomethane in the presence of oxygen, the usual formation of benzophenone azine is suppressed. The 70 % yield of benzophenone may be attributed to a secondary interaction of benzophenone-*O*-oxide *(108)* with diphenylmethylene [166]. When the photolysis is carried out at −70 °C, 8 % of a "dimeric benzophenone peroxide" *(109)*, which is probably the result of a "head-to-tail" dimerization of the carbonyl-*O*-oxide, is obtained [167]. It is not clear at which stage the multiplicity change of the triplet carbene occurs.



Decomposition of the primary ozonides *(110)* does not yield stable, isolable carbonyl oxides either. It does appear that they are plausible intermediates which occur in the transition of 1,2,3- to 1,2,4-trioxolanes. If the standard value of 35 kcal is taken for the O-O single bond, transformation of *(110)* (cf. Section C 7a) to the ozonide should be accompanied with liberation of 52 kcal.



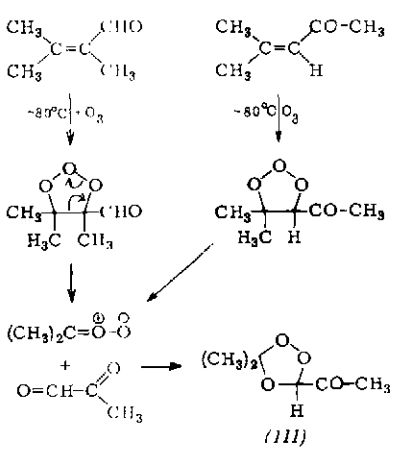
By proper choice of the alkene, combination of the carbonyl oxide with the carbonyl compound may be suppressed, making it possible to study other reactions of these 1,3-dipoles. The spontaneous decomposition of the primary ozonide is presumably a true 1,3-elimination, which as a one step, concerted process forms a counterpart to the 1,3-addition.

b) *Addition to Carbonyl Compounds*

H. Staudinger recognized that the products isolated by *C. Harries* from the reaction of ozone with olefins are cyclic, peroxide-type acetals or ketals [168]. The independent synthesis of 2-butene ozonide from α,α'-dihydroxydiethyl peroxide [169] allows no further doubt that the ozonides are 1,2,4 trioxolanes. According to *R. Criegee*, the ozonides are not formed by intramolecular rearrangement of the primary ozonide, but rather by interaction of the free fragments from the cleavage, as described above. This addition of a carbonyl oxide onto a carbonyl group displays all the properties of a normal 1,3-dipolar cycloaddition.

The yields of ozonide from 1-, 2-, and 3-hexenes, *viz.* 74 %, 30 %, and 32 % [170], show a decline which corresponds to the decrease in dipolarophilic activity, which is observed in the transition from formaldehyde to its higher homologues. It is no less typical that ketones will not add carbonyl oxides, unless the 1,3-dipole and the keto group are part of the same molecule. Tetraalkyl- or tetraarylethylenes generally yield no ozonides, although 1,2-disubstituted cycloalkenes with 5-membered rings form exceptions [171].

Diphenylnitrilimine, benzonitrile oxide, and 3,4-dihydroisoquinoline-*N*-phenylimine do not add onto ordinary ketones, but give adducts with α-keto esters or α-diketones. Similar relationships are encountered here, as indicated by the yield of 60 % ozonide from trimethylacrylic ester [172]; in this case acetone-*O*-oxide adds



[162] *R. Weiss* and *A. Beller*, Mh. Chem. *61*, 143 (1932); *R. Weiss* and *A. Abeles*, ibid. *61*, 162 (1932).

[163] *G. Wittig*, *E. Knauss*, and *K. Niethammer*, Liebigs Ann. Chem. *630*, 10 (1960).

[164] *G. Wittig* and *A. Krebs*, Chem. Ber. *94*, 3260 (1961); *G. Wittig* and *R. Pohlke*, ibid. *94*, 3276 (1961).

[165] *C. D. Nenitzescu*, *M. Avram*, *I. G. Dinulescu*, and *G. Mateescu*, Liebigs Ann. Chem. *653*, 79 (1962); *M. P. Cava* and *R. Pohlke*, J. org. Chemistry *27*, 1564 (1962).

[166] *W. Kirmse*, *L. Horner*, and *H. Hoffmann*, Liebigs Ann. Chem. *614*, 19 (1958).

[167] *P. D. Bartlett* and *T. G. Traylor*, J. Amer. chem. Soc. *84*, 3408 (1962).

[168] *H. Staudinger*, Ber. dtsch. chem. Ges. *58*, 1088 (1925).

[169] *A. Rieche*, *R. Meister*, and *H. Sauthoff*, Liebigs Ann. Chem. *553*, 187 (1942).

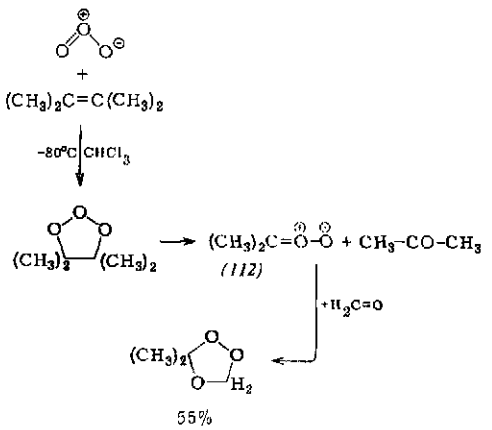
[170] *R. Criegee*, *A. Kerckow*, and *H. Zinke*, Chem. Ber. *88*, 1878 (1955).

[171] *R. Criegee* and *G. Lohaus*, Chem. Ber. *86*, 1 (1953); Liebigs Ann. Chem. *583*, 12 (1953).

[172] *R. Criegee*, *S. S. Bath*, and *B. v. Bornhaupt*, Chem. Ber. *93* 2891 (1960).

onto methyl pyruvate. Halogen in the α-position also activates the carbonyl group sufficiently so as to undergo addition (cf. Section B 3c). Thus, 1,4-dibromo-2,3-dimethyl-2-butene yields 58% ozonide with bromoacetone being formed as the carbonyl component from the primary ozonide. The fact that trimethylacrolein and mesityl oxide form the same ozonide *(111)* is due to the superior dipolarophilic activity of the aldehyde compared with the keto group [172].

More convincing proof of the complete separation of the carbonyl oxide and the carbonyl compound during spontaneous decomposition of primary ozonides is afforded by intermolecular competitive reactions. Thus, ozonization of tetramethylethylene in the presence of formaldehyde leads to isobutene ozonide [173]. This indicates that the acetone-*O*-oxide *(112)* which is formed does not add to the acetone, but rather onto the admixed formaldehyde.



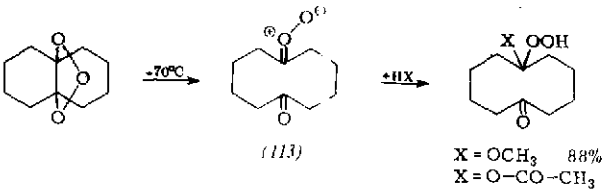
The ozonides of alkenes which are not symmetrical with respect to the double bond can undergo 1,3-elimination in two directions and thus furnish corresponding pairs of carbonyl oxides and carbonyl compounds. Almost no quantitative data are available on the effects of the nature and number of substituents on the direction of cleavage, with the exception of a recent study of substituted *cis*-dibenzoylethylenes [174]. A general tendency towards formation of conjugated aldehydes or ketones as cleavage fragments is discernible.

c) *Dimerization and Reactions with HX*

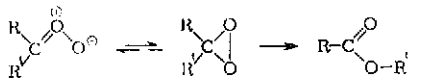
Benzophenone-*O*-oxide *(108)*, which is formed from the primary ozonide of tetraphenylethylene, is unable to add onto benzophenone, but instead dimerizes to the cyclic peroxide *(109)*; the latter can also be obtained from benzophenone and H_2O_2 [175].

It is interesting that *Staudinger* [168] had already postulated decomposition of primary ozonides to carbonyl oxides in order to account for the formation of dimeric ketone peroxides in the side reaction which frequently takes place during ozonide formation. Dimeric or trimeric ketone peroxides become the main product when ozone is allowed to react with alkenes which are not capable of ozonide formation [176].

In a protonated solvent, HX, the dimerization of carbonyl oxides is completely suppressed in favor of an addition of HX. The behavior of the carbonyl oxide *(113)*, obtained from Δ⁹-octalin [176], may be given as an example.



Finally, the rearrangement into carboxylic esters is one of the peculiarities of the carbonyl oxide system. This occurs when the central carbon atom carries substituents which migrate easily. A simplified interpretation is offered by the assumption of an intermediate *(114)*. A close mechanistic relationship with the rearrangement occurring in the Baeyer-Villiger reaction of ketones with peracids is readily recognized [177].



On ozonolysis of 2,4,6-trimethoxycinnamic ester and subsequent hydrolysis, one obtains 48% trimethoxyphenol along with only 8% 2,4,6-trimethoxybenzaldehyde [178]. This large migratory aptitude of the trimethoxyphenyl residue is reminiscent of other rearrangements. The peracid cleavage of α-diketones between the carbonyl groups has its counterpart in the migration of the acyl group of acylated carbonyl oxides which leads to carboxylic anhydrides [179].

7. Ozone

Combination of an oxygen atom with the O_2 molecule yields the triatomic modification - ozone. Analysis of the microwave spectrum of ozone reveals two bonds of equal length (1.28 Å) enclosing an angle of 117°.

This length is intermediate between those associated with single and double O–O bonds [180]. This, as well as the electric moment of 0.53 D indicates a mesomeric ground state in which ozone may be regarded as a 1,3-dipole.

Despite the high oxidation potential of ozone, its reactions with organic compounds display considerable specificity. The oxidation of tertiary amines to amine oxides and of sulfides to sulfoxides and sulfones is readily explained as an electrophilic attack by the outer oxygen.

In the several examples given above, the initial interaction of ozone with alkenes has been formulated as a 1,3-dipolar addition. In the following Section proof will be furnished that the primary ozonides are 1,2,3-trioxolanes.

[173] *R. Criegee, G. Blust,* and *H. Zinke,* Chem. Ber. *87,* 766 (1954).

[174] *P. S. Bailey, S. B. Mainthia,* and *C. J. Abshire,* J. Amer. chem. Soc. *82,* 6136 (1960).

[175] *C. S. Marvel* and *V. Nichols,* J. org. Chemistry *6,* 296 (1941).

[176] *R. Criegee* and *G. Wenner,* Liebigs Ann. Chem. *564,* 9 (1949); *R. Criegee* and *G. Lohaus,* ibid. *583,* 6 (1953).

[177] Review: *C. H. Hassall,* Org. Reactions *9,* 73 (1957).

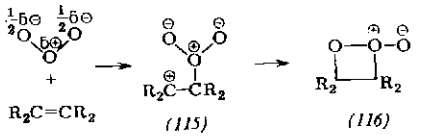
[178] *E. Späth, M. Pailer,* and *G. Gergely,* Ber. dtsch. chem. Ges. *73,* 795 (1940).

[179] *R. Criegee, P. de Bruyn,* and *G. Lohaus,* Liebigs Ann. Chem. *583,* 19 (1953).

[180] *R. Trambarulo, S. N. Ghosh, C. A. Burrus,* and *W. Gordy* J. chem. Physics *21,* 851 (1953).

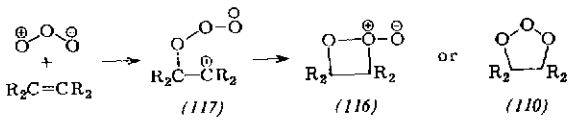
a) *Constitution of Primary Ozonides*

When *H. Staudinger* [168] proposed structure *(116)* for the hypothetical "molozonides", it may have been for the simple reason that the different oxygen functions encountered in ozonides are preformed in that formula. The retention of this formula until recently may be attributed chiefly to the unwarranted conclusion that the positive end of the ozone dipole, *i.e.* the middle oxygen atom, is the one which makes the electrophilic attack on the olefinic or aromatic bond [181]. The subsequent cyclization to form a 4-membered ring *(116)* then becomes necessary to balance the charges.



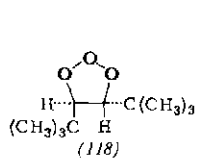
(115) *(116)*

Such a relationship between formal charge and electrophilicity does not exist in practice. Even if a primary electrophilic attack does occur, attack of the outer ozone oxygen [182] to form *(117)* could be accomplished with a far less drastic charge separation in the carbonium ion intermediate than that indicated by *(115)*. However, intermediate *(117)* can lead to closure of a 4- or a 5-membered ring. No evidence is available to indicate the existence of the 4-membered ring; moreover, the 1,2,3-trioxolane structure has the advantages of a lower ring strain and lack of a formal charge.

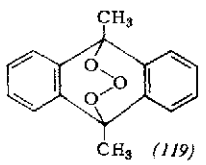


(117) *(116)* or *(110)*

The very existence of a cyclic primary ozonide has often been questioned. Even in 1957, a hypothesis has been considered in which a π-complex obtained from ozone and an alkene rearranged directly to a carbonyl oxide and an aldehyde [183]. In 1960, *R. Criegee* and *G. Schröder* succeeded in isolating a crystalline primary ozonide *(118)* with an intact C–C bond. This compound was obtained from *trans*-1,2-di-t-butylethylene and ozone at −75 °C. When the temperature was raised, it rearranged exothermically to a normal ozonide [184]. An adduct



(118)



(119)

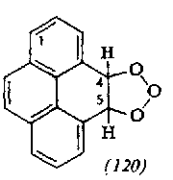
(119) that is stable up to room temperature is formed by the addition of ozone onto 9,10-dimethylanthracene [185]. Since the NMR spectrum of the adduct has only one signal for the methyl protons, it seems that *(119)* contains a 7-membered ring [186].

Thus, after numerous deviations, the consensus of opinion is that the probable structure of the primary ozonide is that expected on the basis of a 1,3-dipolar cycloaddition. Kinetic data strongly support the concept that the formation of the primary ozonide does not occur in two steps, as formulated above, but rather is a genuine one-step 1,3-dipolar addition. Ozonization of aromatic compounds also supplies important information in support of this assumption.

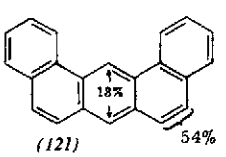
b) *Ozone and Aromatic Compounds*

The rate-determining attack of the first molecule of ozone on benzene yields a cyclohexadiene derivative, which rapidly takes up two additional molecules of ozone. As with all other aromatic ozonides, "benzene triozonide" is probably present not as a monomer, but in polymeric form. Naphthalene takes up two moles of ozone at −40 °C, whereby one ring is destroyed by oxidation and the second retains its benzenoid resonance [187].

Badger has pointed out that the attack of ozone on polycyclic aromatic hydrocarbons takes place not at the carbon atom of greatest electron density, but at the bond exhibiting the highest double bond character [188]. "Bond localization energies" have been calculated for numerous polycyclics [189]. The bond with the lowest value is in fact the first to be cleaved by ozone. Whereas electrophilic substitution of pyrene occurs at position 1, which has the highest electron density, ozonization yields 71% 4-formylphenanthrene-5-carboxylic acid. This corresponds to the primary ozonide *(120)*, since the 4,5 bond of pyrene possesses the lowest localization energy.



(120)



(121)

On treatment with ozone in glacial acetic acid, anthracene yields anthraquinone, presumably via a primary 9,10-ozonide analogous to *(119)*. Thus, not only the *ortho*, but also the *para* localization energies must be considered if the site of the ozone attack is to be predicted correctly. For example, the two position of attack in dibenzo[a,j]anthracene *(121)* agree with expectations [190]. The concept of a "double bond reagent" [188] thus proves fruitful and leads automatically to the

[181] *J. P. Wibaut, F. L. J. Sixma, L. W. F. Kampschmidt*, and *H. Boer*, Rec. Trav. chim. Pays-Bas *69*, 1355 (1950); *F. L. J. Sixma, H. Boer* and *J. P. Wibaut* ibid., *70*, 100 (1951).

[182] *J. Meinwald*, Chem. Ber. *88*, 1889 (1955).

[183] *P. S. Bailey*, Chem. and Ind. *1957*, 1148.

[184] *R. Criegee* and *G. Schröder*, Chem. Ber. *93*, 689 (1960).

[185] *P. de Bruyn*, Bull. Soc. chim. Belg. *69*, 328 (1960).

[186] *R. E. Erickson, P. S. Bailey*, and *J. C. Davis*, Tetrahedron *18*, 388 (1962).

[187] *L. W. F. Kampschmidt* and *J. P. Wibaut*, Rec. Trav. chim. Pays-Bas *73*, 431 (1954).

[188] *G. M. Badger*, Quart. Reviews (London) *5*, 157 (1951).

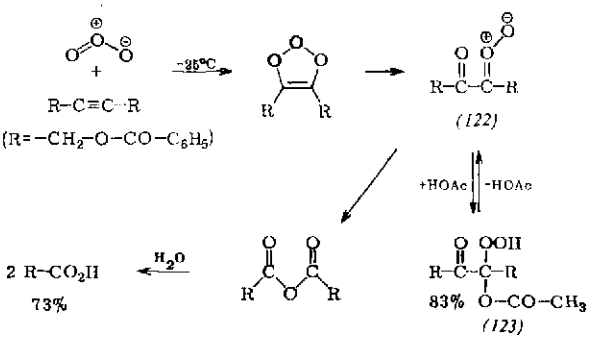
[189] *R. D. Brown*, J. chem. Soc. (London) *1950*, 3249; *M. J. S. Dewar*, J. Amer. chem. Soc. *74*, 3357 (1952).

[190] *E. J. Moriconi, B. Rakoczy*, and *W. F. O'Connor*, J. org. Chemistry *27*, 3618 (1962).

picture of a concerted addition of ozone, in contrast to the electrophilic primary attack suggested earlier.

c) *Addition to Alkynes*

Ozone attacks triple bonds much more slowly than double bonds. Hydrolysis of the reaction products affords high yields of carboxylic acids. Experiments of *R. Criegee* and *M. Lederer* suggest that the primary addition of ozone proceeds in exactly the same way as in the alkene series. Analogous ring opening leads in this case to an acylcarbonyl oxide. The rearrangement described in Section C 6c yields the acid anhydride and, after hydrolysis, two equivalents of carboxylic acid. Ozonization of 2-butyn-1,4-ylene dibenzoate in glacial acetic acid results in formation of the acetic acid adduct *(123)* of the acylcarbonyl oxide [191].

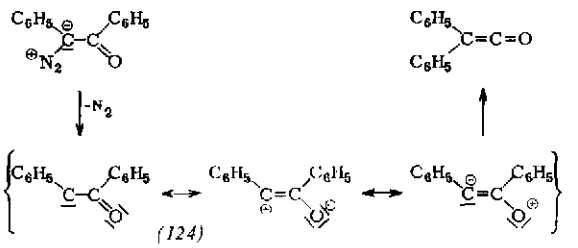


D. Additions of 1,3-Dipoles without Octet Stabilization

The chemistry of 1,3-dipolar systems which are not octet-stabilized (Tables 3 and 4) is in such a state of flux that a systematic treatment is not yet warranted. This is one area where the discovery of surprising new reactions should make future study quite rewarding. Since these systems are for the most part transient intermediates in molecular rearrangements, it is mandatory that the 1,3-additions be carried out *in situ*. Our investigation of ketocarbenes, which served up to now as a model of these 1,3-systems (Table 3), emphasizes the necessity of planning structural variations in the reactants in order to promote intermolecular reactions which can compete with intramolecular rearrangements.

1. Ketocarbenes

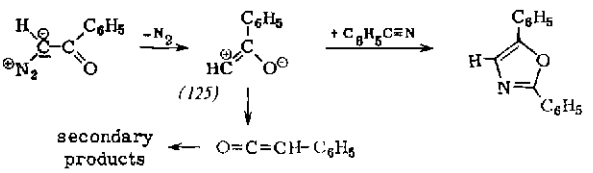
The thermolysis of diazoketones to carboxylic acids, discovered by *L. Wolff*, has found useful application in the Arndt-Eistert method for lengthening the carbon chain of carboxylic acids. In some cases [192], especially when the reaction is carried out photochemically [193], ketenes may be isolated as products of the Wolff rearrangement. The hypothetical intermediate is the ketocarbene with a singlet state which can be described by neutral and zwitterionic resonance structures.



a) *Decomposition of Diazoketones in Benzonitrile*

The diphenylketocarbene *(124)*, which is formed from azibenzil at 70 °C, rearranges extremely rapidly to diphenylketene. It is uncertain that *(124)* occurs at all as a discrete intermediate, as we were unable to trap the ketocarbene as a 1,3-adduct even with active dipolarophiles [194].

However, the isolation of 0.4 % 2,5-diphenyloxazole by thermolysis of diazoacetophenone in benzonitrile at 150 °C provided an initial clue for the ketocarbene intermediate. Besides the Wolff rearrangement to phenylketene, secondary products of which were collected to the extent of over 50 %, also a 1,3-addition of benzoylmethylene *(125)* to the dipolarophilic nitrile group takes place [194].



Metallic copper and some copper(I) and copper(II) compounds not only promote nitrogen liberation from diazoalkanes, but also stabilize carbenes in a manner which is still not understood. Suppression of the Wolff rearrangement of ketocarbenes in the presence of copper is indicated by the fact that in the copper-induced decomposition of diazoketones, olefins are transformed into acylcyclopropanes [195]. It is noteworthy that this tendency, which in the case of benzoylmethylene *(125)* leads to the closure of a 3-membered ring, is superseded in benzonitrile by the formation of a 5-membered ring. In the presence of copper powder, copper(I) cyanide, or copper(II) acetylacetonate, the above reaction yields 16–17 % 2,5-diphenyloxazole [194].

In the case of cyclic diazoketones, the Wolff rearrangement is associated with ring contraction. Photolysis of 4,7-dimethyl-2-diazoindan-1-one *(126)* in aqueous tetrahydrofuran yields 3,6-dimethylbenzocyclobutenecarboxylic acid [196]. The assumption that here the rate of rearrangement is somewhat lower, owing to the

[191] *R. Criegee* and *M. Lederer*, Liebigs Ann. Chem. *583*, 29 (1953).

[192] *G. Schroeter*, Ber. dtsch. chem. Ges. *42*, 2336 (1909); *H. Staudinger* and *H. Hirzel*, ibid. *49*, 2522 (1916).

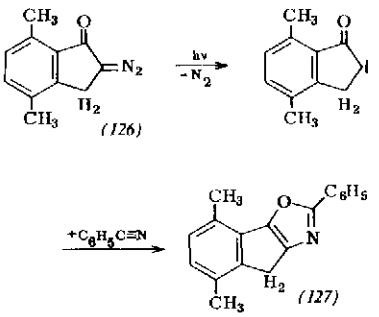
[193] *L. Horner* and *E. Spietschka*, Chem. Ber. *85*, 225 (1952).

[194] *R. Huisgen*, *H. König*, *G. Binsch*, and *H. J. Sturm*, Angew. Chem. *73*, 368 (1961).

[195] *J. Novak*, *J. Ratusky*, *V. Sneberk*, and *F. Sorm*, Chem. Listy *51*, 479 (1957); Chem. Abstr. *51*, 10508 (1957).

[196] *M. P. Cava*, *R. L. Litle*, and *D. R. Napier*, J. Amer. chem. Soc. *80*, 2257 (1958); cf. *L. Horner*, *W. Kirmse*, and *K. Muth*, Chem. Ber. *91*, 430 (1958).

increasing ring strain, appears to be correct. The decomposition of *(126)* in benzonitrile with and without copper leads to the isolation of 11 % and 34 %, respectively, of the condensed oxazole *(127)* [197].

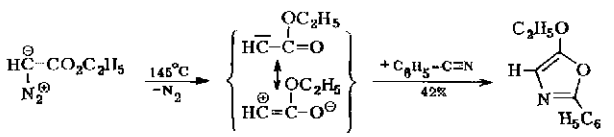


(126) *(127)*

b) *1,3-Additions of Ethoxycarbonylcarbene*

Loss of nitrogen from ethyl diazoacetate produces ethoxycarbonylcarbene *(128)*, which is incapable of undergoing Wolff rearrangement. It would be expected that the mesomerism of the carboxylic ester would tend to oppose the 1,3-dipolar activity which the compound should exhibit as a ketocarbene. The decomposition of diazoacetic ester in olefins or aromatics does in fact produce cyclopropanecarboxylic esters.

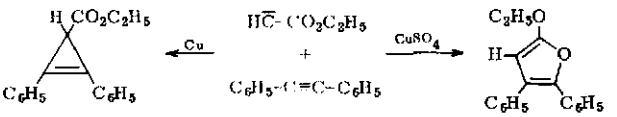
Surprisingly, however, we obtained 42 % 2-phenyl-5-ethoxyoxazole [194] by thermolysis of diazoacetic ester in benzonitrile. It is conceivable that *(128)* first combines



(128)

with the nitrile group to give an azirine-3-carboxylic ester, and that the 3-membered ring is then enlarged to a 5-membered one during a subsequent rearrangement. This hypothesis cannot be tested as long as such acylated azirines are unknown. However, it is more probable that 1,3-dipolar addition occurs, leading directly to an aromatic system. Acetonitrile and phenylacetonitrile also react with *(128)* to give 2-substituted 5-ethoxyoxazoles.

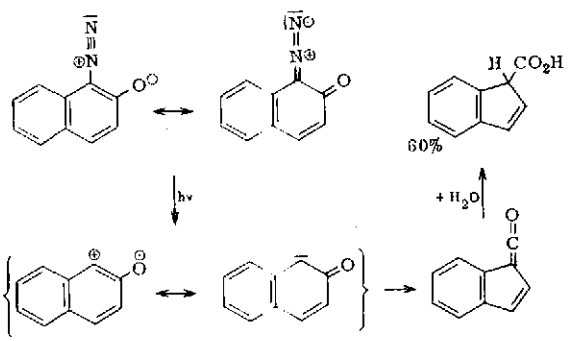
A noteworthy but still mysterious dependence on the nature of the catalyst used to induce decomposition of diazoacetic ester is shown by the products obtained with tolane. A cyclopropene derivative is formed in the presence of copper powder [198], while the use of copper sulfate leads to an isomer which is suggested to be 2-ethoxy-4,5-diphenylfuran [199]. The tendency of the ethoxycarbonylcarbene to react at the 1,1- or the 1,3-position needs further clarification. For example, the reaction of diazoacetophenone with tolane in the presence of copper yields 2,3,5-triphenylfuran [197].



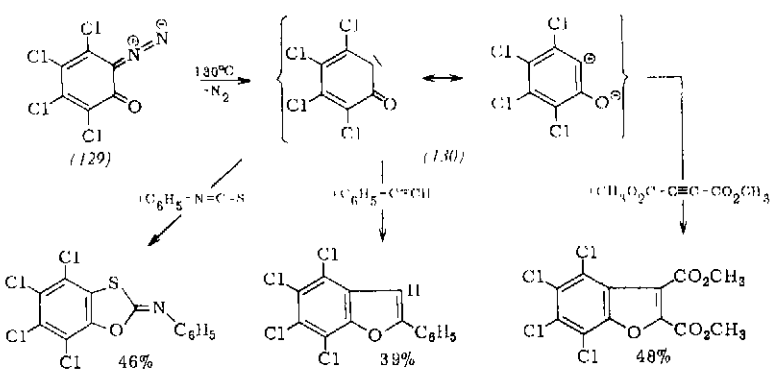
Trifluoroacetylethoxycarbonylcarbene likewise shows no tendency to undergo a Wolff rearrangement. The formation of 1:1 adducts with acetonitrile and acetone has recently been described [200].

c) *Additions of Aromatic Ketocarbenes*

Like the aliphatic diazoketones, *o*-diazo-oxides of the aromatic series are capable of undergoing Wolff rearrangement. Photolysis of the CN bond is followed by a ring contraction to yield the cyclopentadienoketene derivative [201]. The aromatic ketocarbene, which occurs here as an intermediate, loses its aromaticity on rearrangement; this should result in an increased lifespan of the intermediate.



In tetrachlorobenzene-*o*-diazo-oxide *(129)*, the stability of the carbenoid intermediate increases to such an extent that photolysis in methanol yields 70 % tetra-



(129) *(130)*

[197] *G. Binsch*, Ph.D. Thesis, Universität München, 1963.

[198] *R. Breslow, R. Winter*, and *M. Battiste*, J. org. Chemistry *24*, 415 (1959).

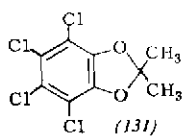
[199] *I. A. Dyakonow, M. I. Komendantov, I. Gokhmanova*, and *R. Kostikov*, Zh. obshch. Khim. *29*, 3848 (1959); Chem. Abstr. *54*, 19521 (1960); *R. Breslow* and *D. Chipman*, Chem. and Ind. *1960*, 1105.

[200] *F. Weygand, H. Dworschak, K. Koch*, and *S. Konstas*, Angew. Chem. *73*, 409 (1961).

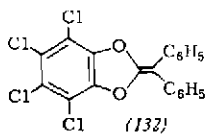
[201] *O. Süs*, Liebigs Ann. Chem. *556*, 65, 85 (1944).

chloroguaiacol [197]. Thermolysis of *(129)* in phenylacetylene at 130 °C leads to a 39% yield of the 1:1 adduct of ketocarbene *(130)* with the solvent. The structure of the adduct has been elucidated to be that of 2-phenyl-4,5,6,7-tetrachlorobenzo[*b*]furan [194]. Decomposition in styrene gives the 2,3-dihydro derivative of the adduct just mentioned, while in dimethyl fumarate a 60% yield of dihydrobenzo[*b*]furandicarboxylic ester is obtained.

Thermolysis and photolysis of *(129)* give nearly identical results. The addition of *(130)* onto benzonitrile is accompanied by closure of the oxazole ring. When the reaction is undertaken in phenyl isothiocyanate, the C=S double bond displays the greater dipolarophilic activity. On addition to carbon disulfide, 80% of a crystalline adduct may be isolated. Diazo-oxides which readily undergo ring contraction to cyclopentadienoketenes are also able to participate in 1,3-cycloadditions onto carbon disulfide [194,197]. Photolysis of *(129)* in acetone results in addition of *(130)* onto the ketonic carbonyl group yielding 30% of the 1,3-benzodioxole *(131)*.



(131)



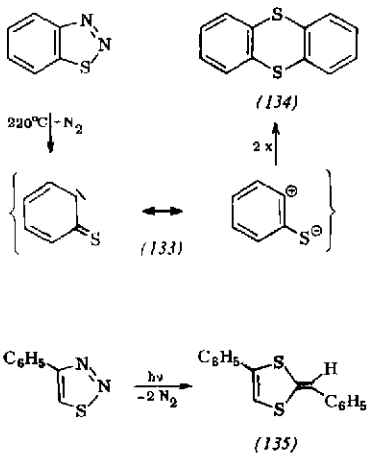
(132)

The decomposition rate of the *o*-diazo-oxide *(129)* depends only slightly on the solvent. This is evidence that reaction with the dipolarophile begins only after loss of the nitrogen; thus, the reactions really involve the aromatic ketocarbene *(130)*. However, the reaction of diphenylketene with *(129)* follows a completely different mechanism. The liberation of nitrogen even below 100 °C indicates an induced decomposition. Hence, the adduct *(132)*, obtained in 50% yield, is not the result of a 1,3-dipolar addition of the ketocarbene [194]. It may be presumed that the initial step is acylation of the oxygen of the diazo-oxide. The reaction of *o*-diazo-oxides with ketenes has also been investigated elsewhere [202].

In addition, it may be remarked that ketocarbene *(130)* also has the ability to enter into aromatic substitutions and to detach hydride ions [197].

2. Thioketocarbenes

The formation of thianthrene *(134)* by thermolysis of 1,2,3-benzothiadiazole [203] is in agreement with a mechanism stipulating dimerization of the intermediate aromatic thioketocarbene *(133)*. The generation of the dithiafulvene derivative *(135)* by photolysis of 4-phenyl-1,2,3-thiadiazole, which has been reported by *Kirmse* and *Horner* [204], also indicates a 1,3-addition of phenylthioketocarbene onto the phenylthioketene, which is the product of Wolff rearrangement.

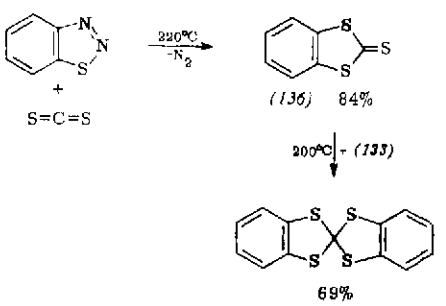


(134)

(133)

(135)

Compared with the aromatic ketocarbene *(130)*, the thio analogue *(133)* displays surprisingly sluggish reactivity. This is manifested, for example, in the fact that dimerization to *(134)* during decomposition of 1,2,3-benzothiadiazole in fumaric ester, naphthyl isocyanate, or benzonitrile cannot be suppressed. Only C=S double bonds seem capable of combining with the 1,3-dipolar system *(133)*. When benzothiadiazole is heated with carbon disulfide in an autoclave at 220 °C, the product is 1,3-benzodithiol-2-thione *(136)*, which has a C=S double bond capable of adding on another molecule of *(133)* [205].



(136) 84%

69%

Coupling of *(133)* with the C=S double bond in phenyl isothiocyanate also proceeds smoothly. Photolysis of 1,2,3-thiadiazole should give the parent compound of the thioketocarbene series; however, its addition onto carbon disulfide is not very productive [205].

3. Some 1,3-Dipolar Systems without a Double Bond

Gulbins and *Hamann* [206] produced isolable oxazolidin-2-ones by heating mixtures of isocyanates with epoxides, ethylene carbonate, ethylene sulfite, or their derivatives. Since the presence of isocyanates did not lower the decomposition temperature of ethylene carbonate appreciably, it appears possible that the reaction produces as the initial product an open-chain 1,3-dipole which is

[202] *P. Yates* and *E. W. Robb*, J. Amer. chem. Soc. *79*, 5760 (1957); *W. Ried* and *R. Dietrich*, Liebigs Ann. Chem. *639*, 32 (1961); Naturwissenschaften *47*, 445 (1960).

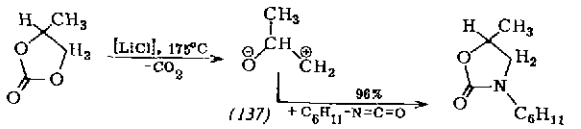
[203] *P. Jacobson* and *H. Janssen*, Liebigs Ann. Chem. *277*, 209, 218 (1893).

[204] *W. Kirmse* and *L. Horner*, Liebigs Ann. Chem. *614*, 4 (1958).

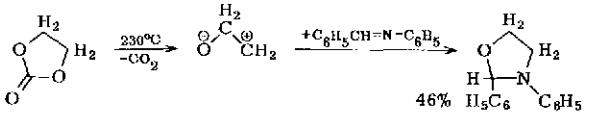
[205] *R. Huisgen* and *V. Weberndörfer*, Experientia *17*, 566 (1961).

[206] *K. Gulbins*, *G. Benzing*, *R. Mayschölder*, and *K. Hamann*, Chem. Ber. *93*, 1975 (1960); *K. Gulbins*, *M. Roth*, and *K. Hamann*, Angew. Chem. *73*, 434 (1961); cf. *G. P. Speranza* and *W. J. Peppel*, J. org. Chemistry *23*, 1922 (1958); *M. L. Weiner*, ibid. *26*, 951 (1961).

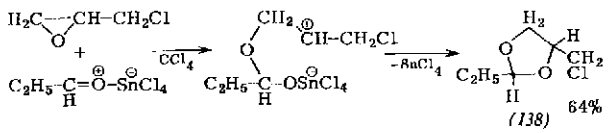
not octet-stabilized, *e.g. (137)*, and which then in turn adds to the isocyanate. Catalysis with lithium chloride reduces the temperature of this reaction from 240 °C to



180 °C. Thermolysis of ethylene carbonate in *N*-benzylideneaniline yields similarly a 1:1 adduct, *viz.* 2,3-diphenyloxazolidine [207].

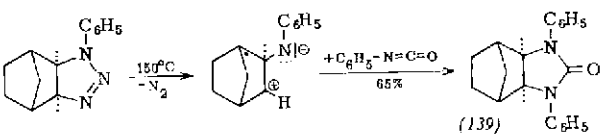


On the other hand, it appears doubtful whether a true 1,3-dipolar cycloaddition is still operative in the reaction of epoxides and aldehydes at room temperature catalysed by stannic tetrachloride which leads to 1,3-dioxolanes of type *(138)* [208]. The electrophilic nature of the catalysts makes other reaction paths possible, one of which is formulated in the accompanying reaction scheme. The carbonyl groups of ethyl formate and of γ-butyrolactone are also suitable acceptors [209].



Finally, ethylene, propylene, styrene oxides, and epichlorohydrin react with ketene under the influence of boron trifluoride to give low yields of γ-lactones [210]. The analogous additions onto the C≡C triple bond of ethyl phenylpropiolate are likewise not very productive [211].

The *N*-analogue of this 1,3-dipole should be formed by thermolytic evolution of nitrogen from Δ²-1,2,3-triazolines (Section B 5b). Preliminary studies in our laboratory support this expectation. Decomposition of the phenyl azide-norbornene adduct in phenyl isocyanate at 150 °C yields the isolable bicyclic diphenylurea derivative *(139)*



[116]. However, the 1,3-dipolar addition mechanism can be considered as proven only if kinetic data exclude the possibility of an induced decomposition of the triazoline.

[207] *E. Stelter*, Diploma Thesis, Universität München, 1960.

[208] *Th. Bersin* and *G. Willfang*, Ber. dtsch. chem. Ges. *70*, 2167 (1937); *G. Willfang*, ibid. *74*, 145 (1941).

[209] *H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert, K. W. Müller, H. J. Sasse, H. Schrodt*, and *J. Spille*, Angew. Chem. *67*, 374 (1955); *K. Bodenbenner*, Liebigs Ann. Chem. *623*, 183 (1959).

[210] *R. Oda, S. Muneimiya*, and *M. Okano*, J. org. Chemistry *26*, 1341 (1961).

[211] *R. Huisgen* and *J. A. Zoltewicz*, unpublished results.

E. Future Prospects

The 1,3-dipolar addition is extremely versatile. The range of synthetic possibilities which it opens is so large that it may well equal the importance of the Diels-Alder synthesis.

Extending previous work, mainly on nitrile oxides, diazoalkanes, azides, and ozone, over the past five years, our Munich laboratory group has conducted a preliminary survey of the applicability of 3 + 2 → 5 cycloadditions by preparing and analyzing more than 1000 adducts. Some octet-stabilized 1,3-dipoles and the majority of nonoctet-stabilized 1,3-dipolar systems still await discovery.

Even today, 1,3-dipolar cycloadditions allow the preparation of a large number of 5-membered heterocycles. A series of especially acid-labile or thermolabile ring systems were prepared for the first time by this route. The fact that the numerous individual reactions studied are patterned after a single principle, not only in a formal but also in a mechanistic sense, is most satisfying. The features of the mechanism will form the subject of a publication to appear shortly in this journal.

Many of the new 1,3-dipoles are represented thus far by more or less exceptional structural types, if not indeed chemical curiosities. This fact is due to our desire to acquire rapidly representatives of the new classes of dipoles and to test their ability to undergo cycloaddition. The development of general synthetic routes leading to 1,3-dipoles will have to receive closer attention in future studies.

It gives me great pleasure to express my sincere thanks to my excellent scientific associates: K. Adelsberger, Dr. K. Bast, Dr. H. O. Bayer, R. Bermes, Dr. G. Binsch, Dr. J. M. Craven, Dr. A. Eckell, Dr. R. Fleischmann, Dr. M. V. George, Dr. H. Gotthardt, H. Hauck, Dr. A. S. Kende, R. Knorr, H. Knupfer, Dr. H. König, Dr. R. Krischke, Dr. P. Laur, Dr. W. Mack, Dr. L. Möbius, Dr. R. M. Moriarty, Dr. G. Müller, R. Raab, R. Schiffer, Dr. M. Seidel, H. Seidl, Dr. H. Stangl, E. Steingruber, E. Stelter, G. Szeimies, Dr. G. Wallbillich, V. Weberndörfer, Dr. F. Wimmer, and Dr. J. A. Zoltewicz. The essential role played by Dr. R. Grashey, who accompanied me for the greater part of the journey into these uncharted regions, must be emphasized. The contribution of our technical assistants, namely Mmes. and Messrs. H. Huber, E. Kudera, H. Leitermann, R. Schmidt, E. Spindler, H. Wagenhofer, and I. Wimmer is also acknowledged. I am much indebted to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for their support of this program.

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Nitrenes

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Nitrenes are molecular fragments with six electrons on the nitrogen which are formed thermally or photochemically from hydrazoic acid or organic azides. Kinetics of the cleavage of azides, spectroscopic data, and electron spin resonance measurements constitute proof for the biradical nature of the nitrenes studied. As a result of hydrogen shifts, nitrenes are capable of isomerization to imines, of hydrogen abstraction from neighboring molecules affording primary amines, and of ring formation by internal dehydrogenation (insertion reactions). Isomerization and hydrogen shifts are observed primarily with alkylnitrenes; however, under favorable structural conditions, hydrogen shifts in arylnitrenes also lead to imines. Arylnitrenes dimerize to azo compounds and undergo intra- and intermolecular reactions with nucleophilic reactants. Thus, both stable and unstable acylnitrenes, which are formed thermally or photolytically from acyl azides, add on, for example, to dimethyl sulfide or dimethyl sulfoxide, affording sulfimines or sulfoximines, respectively. Nucleophilic reagents, such as alcohols and amines, also react with nitrenes. Besides azides, anil-N-oxides also undergo cleavage to give nitrenes. The reaction of N-chloramines and hydroxylamine-O-sulfonic acids with nucleophilic reagents probably does not proceed via a nitrene intermediate, but rather by an S_N mechanism. A crucial experiment differentiating between these two paths is described, and Raschig's hydrazine synthesis is discussed in detail.

1. Introduction

Detachment of low-energy decomposition products constitutes a very useful method of forming high-energy uncharged molecular fragments containing an electron sextet. Thus, carbenes are formed by thermal or photochemical elimination of N_2 or CO from diazoalkanes or ketenes respectively, or by α-elimination of hydrogen halide from halogenoalkanes by the action of strong bases [1]. Correspondingly, *ortho*-substituted aromatic compounds can be converted into arynes [2] and molecular fragments with electron deficiency in the 1- or 3-position which can undergo dipolar 1,3-additions [3]. The fragments containing an electron sextet are very reactive; they can be trapped by addition or insertion reactions.

Closely related to the carbenes are the derivatives of univalent nitrogen, *i.e.* the nitrenes. Carbenes and nitrenes are isoelectronic. They can be formed and detected by similar methods. The search for further common characteristics of carbenes and nitrenes and for potential preparative applications has resulted in considerable progress in nitrene chemistry in recent years.

The terminology used to denote the R–$\overline{N}$: fragments is not uniform. In 1959, *Lüttringhaus*, *Jander*, and *Schneider* [4] suggested the term "imene" because it is easy to remember in analogy to carbene. *Appel* and *Buchner* [5] and we ourselves [6] support this suggestion. To avoid misunderstandings, the terms imyne [1], imine radical [7,8], phenyl nitrogen for C_6H_5N [9], and electron-deficient nitrogen should not be used in future. The terms azene [10,11] and nitrene [12–14] are used in the Anglo-American literature.

For the sake of completeness, it should be noted here that *Staudinger* [15] originally used the term imenes to denote iminoketenes, $R_2C{=}C{=}NR$, which were first prepared by him. Later he changed this term to ketenimine [16].

2. Formation, Properties, and Detection of Nitrenes

a) Nitrenes from Azides [17]

Azides, including hydrazoic acid, are as capable as diazo compounds of losing nitrogen thermally, by electric discharge, or by the action of light. Azides yield nitrenes *(1)*, whereas diazo compounds give carbenes *(2)*.

[1] An excellent review can be found in the articles by *W. Kirmse*, Angew. Chem. *71*, 537 (1959); *73*, 161 (1961).

[2] *R. Huisgen* and *J. Sauer*, Angew. Chem. *72*, 91 (1960).

[3] *R. Huisgen* in: 10 Jahre Fonds der Chemischen Industrie zur Förderung von Forschung, Wissenschaft und Lehre, 1950–1960. Verband der Chemischen Industrie, Düsseldorf 1960, p. 73.

[4] *A. Lüttringhaus*, *J. Jander*, and *R. Schneider*, Chem. Ber. *92*, 1756 (1959).

[5] *R. Appel* and *W. Büchner*, Chem. Ber. *95*, 849 (1962).

[6] *L. Horner* and *A. Christmann*, Chem. Ber. *96*, 388 (1963).

[7] *F. O. Rice* and *Th. A. Luckenbach*, J. Amer. chem. Soc. *82*, 2681 (1960).

[8] *J. F. Heacock* and *M.T. Ednison*, J. Amer. chem. Soc. *82*, 3460 (1960).

[9] *M. Appl* and *R. Huisgen*, Chem. Ber. *92*, 2961 (1959).

[10] *G. Smolinsky*, J. Amer. chem. Soc. *83*, 2489 (1961).

[11] *P.A.S. Smith* and *J.H. Hall*, J. Amer. chem. Soc. *84*, 480 (1962).

[12] *G. Smolinsky*, J. Amer. chem. Soc. *82*, 4717 (1960).

[13] *D. H. R. Barton* and *L. R. Morgan*, jr., J. chem. Soc. (London) *1962*, 622.

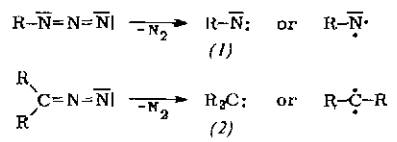
[14] The term nitrene, used by *H. Staudinger* and *K. Miescher* to denote carbon analogues of the nitro group [Helv. chim. Acta *2*, 554 (1919)], is once more available for use, since *C. H. Hassall* and *A. E. Lippman* have elucidated the real structure of the former nitrenes [J. chem. Soc. (London) *1953*, 1059].

[15] *H. Staudinger*, Liebigs Ann. Chem. *356*, 51 (1907).

[16] *H. Staudinger* and *J. Meyer*, Ber. dtsch. chem. Ges. *53*, 72 (1920).

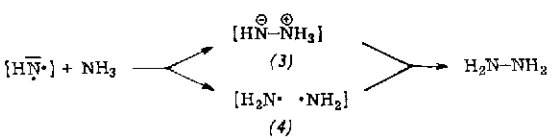
[17] The preparation and properties of organic azides have been reviewed by *J. H. Boyer* and *F. C. Canter*, Chem. Reviews *54*, 35 (1954).

There is no doubt today that nitrenes are real intermediates, and that the isolated reaction products to which they give rise are not formed directly from the azides via excited states. As early as 1928, *Beckman* and *Dickinson*

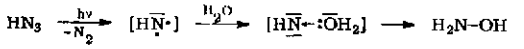


reported [18a] that photochemical decomposition of hydrazoic acid yields hydrogen, nitrogen, and ammonia [18b]. The existence of free NH was first shown spectroscopically by its absorption at 3360 Å by *Franck* and *Reichardt* [19] on high-temperature (2000 °C) pyrolysis of ammonia. However, the most convincing indication was given by the findings of *Keyser* [20], who photolysed hydrazoic acid which was frozen under argon at 4.2 °K and was able to demonstrate the formation of NH by ultraviolet spectroscopy. The ultraviolet spectrum also showed an NH_2 band that was 200 times less intense. The NH_2 radical is believed to have arisen by reaction of NH with a neighboring molecule of hydrazoic acid.

Some important work by *Rice* [21] was performed a few years earlier. He decomposed hydrazoic acid thermally (1000 °C/0.02–2 mm), photochemically, and by a silent electric discharge and obtained a blue deposit on condensing the cleavage products with liquid nitrogen. Despite intense investigations, the nature of this blue product has not yet been elucidated [7]. The deep-blue color of this paramagnetic substance disappears irreversibly on warming to −125 °C, and colorless ammonium azide is formed without evolution of gas. According to *Wannagat* and *Kohnen* [22], this azide contains small amounts of hydrazinium azide. The same authors showed that the yield of hydrazine is increased five- to ten-fold if ammonia is added to the gaseous decomposition products immediately after these have emerged from the decomposition zone. It is not yet known whether the hydrazine is formed via an *N*-imine *(3)* (in analogy to *N*-oxides)



followed by a prototropy or via amino radicals *(4)*. The photochemical decomposition of hydrazoic acid into hydroxylamine and nitrogen in acidic aqueous solution observed by *Gleu* [23] supports the first route.



The elucidation of the structure of the blue product is complicated by the fact that all operations must be carried out below −125 °C and that so far no suitable solvent has been found that is liquid at −125 °C. The blue material is presumably a polymer of NH of unknown molecular weight. *Wannagat* [24] assumed that it is an ozone analogue, *viz.* $HN^{\oplus}-N^{\ominus}-NH=NH$. A blue compound is also obtained on photolysis of solid chloramine at −190 °C [25]. These findings and the spectroscopic detection of the NH_2 radical [20] lead to the conclusion that the NH initially formed can undergo reactions involving transfer of one or two electrons. A similar dualism is observed in the reaction of tertiary amines with diacyl peroxides [26]. The problems of hydrazine formation from ammonia and chloramine are discussed in Section 4.

The question whether nitrenes occur as intermediates has been investigated by *Lwowski* et al. [26a] using flash photolysis of gaseous methyl and ethyl azidoformate. They were able to prove spectroscopically the existence of the nitrene $R-O-CO-\bar{N}\cdot$ which is highly reactive and unstable and immediately combines with suitable compounds such as gaseous cyclohexene. The life-time of the alkoxycarbonylnitrene has been estimated to be several microseconds.

The reactivity of NH is reduced by its combination with organic radicals. This makes it possible to carry out a systematic study of intermolecular reactions of nitrenes with neighboring groups or their rearrangement to stable structures. Thus, photolysis or thermolysis of even methyl azide yields products which permit certain conclusions to be drawn regarding the course of these reactions.

b) Alkylnitrenes from Alkyl Azides

Following the observation [27] that decomposition of methyl azide at 200–240 °C affords nitrogen, hexamethylenetetramine, and ammonia, *Milligan* [28] photolysed methyl azide or trideuteromethyl azide at 4.2 °K in solid argon or at 50 °K in solid carbon dioxide and examined the cleavage products by infrared spectroscopy. Although he was unable to detect the methylnitrene originally formed, he did find methylenimine, which arises from the former as a result of hydrogen migration. Methylenimine is highly reactive and on thawing forms

[18a] *A. O. Beckman* and *R. G. Dickinson*, J. Amer. chem. Soc. *50*, 1870 (1928).

[18b] The quantum yield is a function of the hydrazoic acid pressure; at 2–130 mm, this yield is in the range 3.0–0.5 [18c].

[18c] *A. O. Beckman* and *R. G. Dickinson*, J. Amer. chem. Soc. *52*, 124 (1930).

[19] *H. H. Franck* and *H. Reichardt*, Naturwissenschaften *24*, 171 (1936).

[20] *L. F. Keyser*, J. Amer. chem. Soc. *82*, 5245 (1960); this article contains references to previous work.

[21] *F. O. Rice* and *M. Freamo*, J. Amer. chem. Soc. *73*, 5529 (1951); *75*, 548 (1953); *F. O. Rice* and *Ch. Grelecki*, ibid. *79*, 1880 (1957).

[22] *U. Wannagat* and *H. Kohnen*, Angew. Chem. *69*, 783 (1957).

[23] *K. Gleu*, Ber. dtsch. chem. Ges. *61*, 702 (1928).

[24] *U. Wannagat*, Angew. Chem. *71*, 531 (1959).

[25] *J. Jander* and *J. Fischer*, Angew. Chem. *71*, 626 (1959).

[26] *L. Horner* and *B. Anders*, Chem. Ber. *95*, 2470 (1962).

[26a] *R. St. Berry*, *D. Cornell*, and *W. Lwowski*, J. Amer. chem. Soc. *85*, 1199 (1963).

[27] *J. A. Leermakers*, J. Amer. chem. Soc. *55*, 3098 (1933).

[28] *D. E. Milligan* in: Preprints of Papers Read at the Fifth International Symposium on Free Radicals, July 6–7, 1961. Institute of Physical Chemistry, University of Uppsala, Sweden, Almquist and Wiksell, Stockholm 1961.

hexamethylenetetramine and ammonia. According to *de Darwent* [29], the primary product $CH_3-\overline{N}$: can be detected spectroscopically if the photolysis of methyl azide is carried out in the gas phase.

Milligan [28] studied chlorazide ClN_3 by the same method. His spectroscopic findings lead to the assumption that here chloronitrene is the primary product. The green-blue phosphorescence exhibited on warming the deposit (formed by ultraviolet irradiation) after irradiation is discontinued has been attributed to dimerization of chloronitrene to dichlorodiazine Cl_2N_2 or to its decomposition into nitrogen and chlorine.

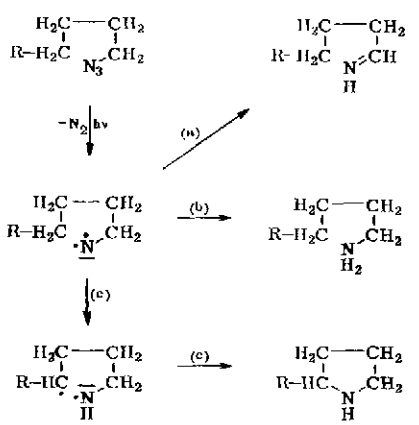
It is known [1] that carbenes are stabilized by insertion into C–H and other bonds as well as by addition onto nucleophilic reagents. Both phenomena are also observed with nitrenes [29a]. However, because of the greater electron affinity of nitrogen compared to carbon, nitrenes have a greater tendency to undergo intramolecular prototropy (imine formation) or to abstract hydrogen from other C–H compounds (*e.g.* solvent). They undergo stabilization by the following reactions:

a) Isomerization to the imine.

b) Hydrogen abstraction from neighboring molecules with formation of a primary amino group.

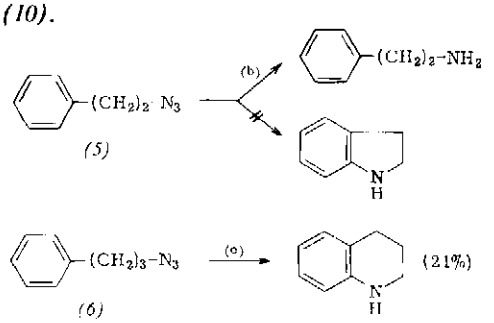
c) Intramolecular hydrogen abstraction with ring closure.

All three stabilization reactions were found by *Barton* and *Morgan* [13] on photolysis of aliphatic azides (Scheme 1).



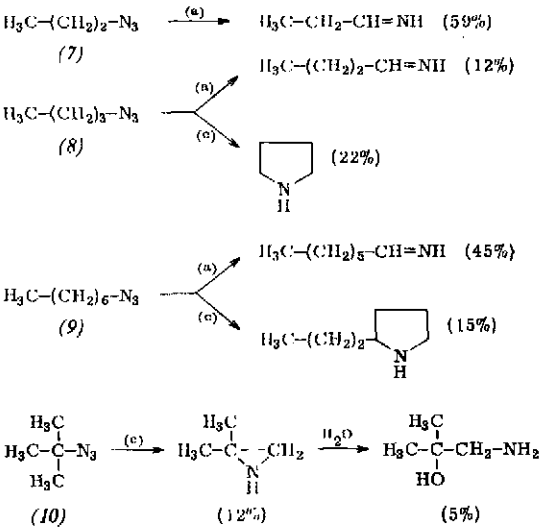
Scheme 1. Pathways leading to the stabilization of an alkylnitrene

These three reaction types also account for the results obtained on photolysis of the alkyl azides *(5)* through *(10)*.

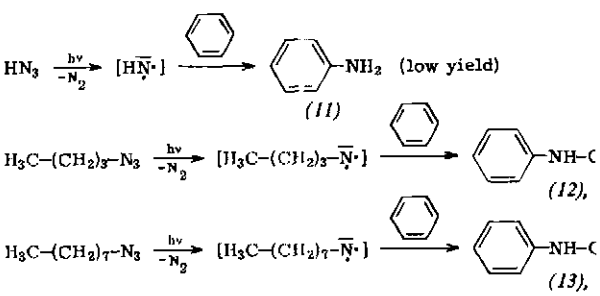


[29] Personal communication to *D. E. Milligan*.

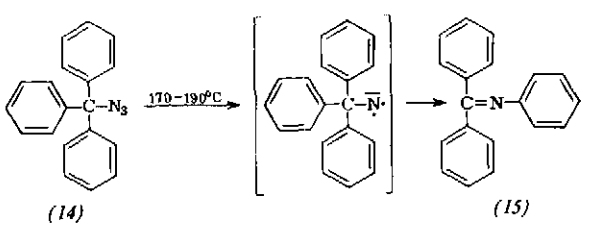
[29a] Compare also the thermolysis of benzylazide in aromatic hydrocarbons and in malonic ester by *Th. Curtius* and *G. Erhart*, Ber. dtsch. chem. Ges. *55*, 1559 (1922).



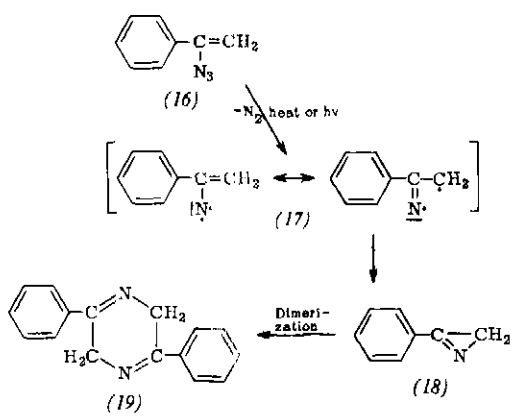
Benzene is attacked by photochemically formed alkylnitrenes as shown by the formation of compounds *(11)* through *(13)*.



Besides hydrogen, aryl groups can also migrate from the α-position to the nitrene nitrogen. This is illustrated by the thermal rearrangement of triphenylmethyl azide *(14)* to the anil of benzophenone *(15)* [30].



If the azido group is attached to a C=C double bond, as in α-azidostyrene *(16)*, then the π-electron pair in the vinylnitrene, which can be formed either thermally



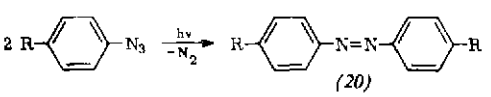
[30] *W. H. Saunders*, jr., and *J. C. Ware*, J. Amer. chem. Soc. *80*, 3328 (1958).

[31a,b] or photolytically [32], migrates to the nitrogen giving rise to 2-phenylazirine *(18)* which dimerizes to a dihydropyrazine *(19)*.

c) Arylnitrenes from Aryl Azides

The chemical behavior of thermally or photolytically formed arylnitrenes is also determined by the electron deficiency on the nitrogen. A more or less pronounced tendency to dimerize to azoarylenes is observed here in addition to intermolecular hydrogen abstraction (*e.g.* reaction with the solvent), intramolecular hydrogen abstraction (followed by ring closure), and addition reactions.

In 1924, *Bertho* [33a, b] showed that thermal decomposition of phenyl azide in aromatic hydrocarbons yields small amounts of azobenzene and aniline in addition to large quantities of resinous products. Photolysis of phenyl azide also affords only traces of azobenzene. However, azo compounds *(20)* can be obtained in good yield from suitably substituted aryl azides [32].

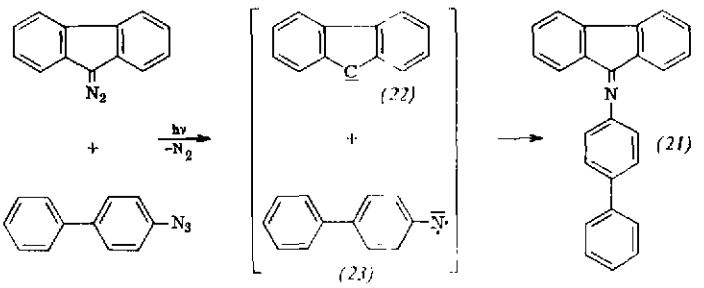


(20)

R = OCH_3, C_6H_5

Column chromatography of the products of pyrolysis of *p*-methoxyphenyl azide resulted in the detection of 2,7-dimethoxyphenazine, *p*-anisidine, and two still unidentified compounds, in addition to the azo compound *(20)* [34].

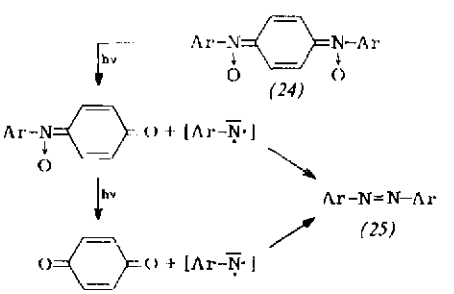
Illumination of equimolar amounts of *p*-methoxyphenyl azide and 4-azidobiphenyl in benzene affords the two symmetrical as well as the mixed azo derivative in nearly equal yields [32]. The fact that irradiation of a mixture of 9-diazofluorene and 4-azidobiphenyl yields 4-fluorenylideneaminobiphenyl *(21)* besides 4,4'-diphenyl-azobenzene, bifluorenylidene, small amounts of fluorenonazine, and bifluorenyl [32] is interesting in that, formally, compound *(21)* may be considered to arise by combination of biphenylenecarbene *(22)* with biphenylylnitrene *(23)*. Biphenylenecarbene *(22)* differs from diphenylcarbene (which dimerizes to tetraphenylethane after hydrogen abstraction from the solvent) in that, in addition to undergoing normal insertion reactions, by analogy to arylnitrenes it can also dimerize to bifluorenylidene [35]. In both biphenylenecarbene and biphenylylnitrene, one electron pair of the electron sextet on the key atom plays a particularly important role. In biphenylenecarbene, it participates in the mesomerism of the ring system; in the arylnitrene it contributes to the greater electron affinity of the nitrogen compared to carbon. The similarity in reactivity of the two compounds also accounts for their ability to combine to give fluorenylidenaminobiphenyl *(21)*. Kinetic analysis will have to be used to show whether the nitrene attacks an intact diazo compound, or the carbene attacks an intact azide with elimination of nitrogen.



(22) *(23)* *(21)*

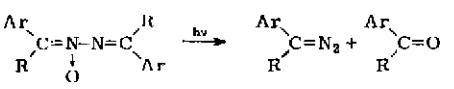
The observations made so far lead to the conclusion that the dimerization of the intermediate arylnitrene to the azo derivative occurs particularly readily in solvents that tend to undergo addition onto atoms with an electron sextet.

Other suitable starting materials for forming arylnitrenes include quinonedianil-*N,N'*-dioxides *(24)*. On exposure to light, they decompose in surprisingly high yield into quinones and arylnitrenes; the latter then dimerize to give azo compounds [36].



(24) *(25)*

Arylnitrenes do not couple to azoaryls in a cage, since on irradiation with filtered light, quinone monoanil-*N*-oxides and azoaryls are also obtained in high yields, and illumination of a mixture of different quinonedianil-*N,N'*-dioxides gives mixed azoaryls. On exposure to light, azine-*N*-oxides *(26)* decompose in an analogous reaction to give carbonyl and diazo compounds [37].



(26)

[31a] *G. Smolinsky*, J. Amer. chem. Soc. *83*, 4483 (1961).

[31b] *G. Smolinsky*, J. org. Chemistry *27*, 3557 (1962).

[32] *L. Horner, A. Christmann*, and *A. Gross*, Chem. Ber. *96*, 399 (1963).

[33a] *A. Bertho*, Ber. dtsch. chem. Ges. *57*, 1138 (1924).

[33b] Cf. also review article by *A. Bertho*, Prakt. Chem. [2], 120, 89 (1929).

[34] *R. Walker* and *W. A. Waters*, J. chem. Soc. (London) *1962*, 1632.

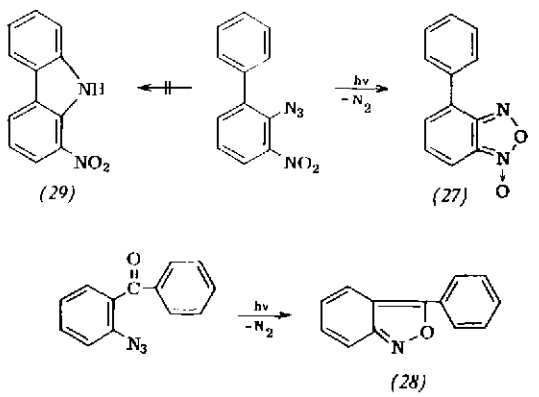
[35] *W. Kirmse, L. Horner*, and *H. Hoffmann*, Liebigs Ann. Chem. *614*, 19 (1958).

[36] *C. J. Pedersen*, J. Amer. chem. Soc. *79*, 5014 (1957).

[37] *L. Horner, W. Kirmse*, and *H. Fernekess*, Chem. Ber. *94*, 279 (1961).

The results of the photolysis of phenyl azide in glacial acetic acid are also consistent with the above representation of the photochemical formation of arylnitrenes from aryl azides. In this case, *p*-acetoxyacetylaniline and *o*-acetaminophenol are formed in addition to large amounts of resinous products. Addition of the nitrene onto the solvent, rearrangement, and acyl migration are the reactions involved [32].

If a group capable of undergoing addition, *c.g.* NO_2 or CO, is located in a suitable position relative to the nitrene nitrogen, ring closure takes place. Thus, 2-azido-3-nitrobiphenyl forms 4-phenylbenzofuroxan *(27)* [38], and 2-azidobenzophenone gives rise to 3-phenylbenzisoxazole *(28)* [39].

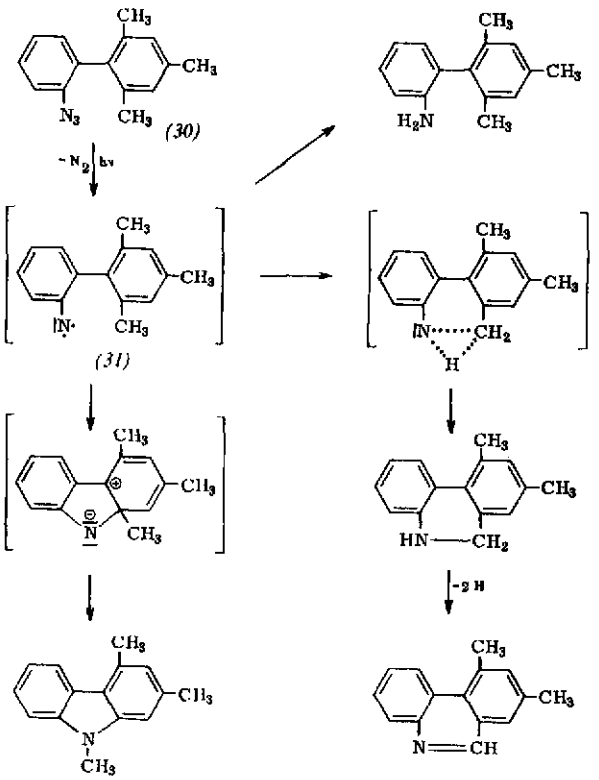


(29) *(27)* *(28)*

The nitro and carbonyl groups are thus more active addition partners than the neighboring benzene ring which, if it participated in this reaction, would give rise to carbazole derivatives *(29)*. These derivatives occur as main products only in the absence of other competing groups [38]. Carbazole formation is still the main reaction when a trimethylphenyl residue occupies the 2-position relative to the azido group *(30)* [10,12]. This reaction is accompanied by dehydrogenation and insertion reactions (Scheme 2). Our own experiments have shown that *o,o'*-diazidobiphenyl does not yield either phenazone or carbazole.

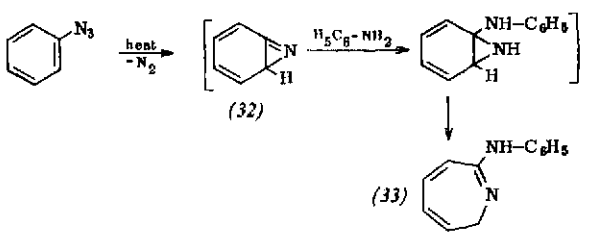
Similar ring closures have been observed on thermolysis (140–180 °C) of *o*-azidodiphenyl sulfide and its sulfone. Products are phenothiazine (32 %) and phenothiazine dioxide (16 %), respectively [39]. *o*-Azidobenzophenone and the corresponding nitrene are reported to occur during thermolysis of *o*-aminobenzophenone, which leads to phenylanthranil [39a].

Decomposition of phenyl azide in a large excess of hot aniline affords a derivative of 7*H*-azepine *(33)* [40a–c]. Photolysis of *p*-anisyl azide in aniline, however, yields azoanisole [32]. The existence of the azirine structure *(32)* as a valence isomer of nitrene has become more



Scheme 2. Stabilization reactions of 2,4,6-trimethylbiphenyl-2'-nitrene *(31)*.

probable as a result of the findings of *Smolinsky* [31,32]. Kinetic measurements [11,40c–42] have shown that aryl azides decompose on thermolysis by a first-order reaction, the elimination of nitrogen being rate-determining.



(32) *(33)*

Smith and *Hall* [11] studied the effect of substituents and determined the enthalpies and entropies of activation. The values for *p*-methoxyphenyl azide and cyclohexyl azide are about 38 and 47 kcal/mole and about 19 and 32 cal/deg/mole, respectively [34]. The rate constants for the evolution of nitrogen show only slight dependence on the type of solvent used and on the substituent, and do not follow the Hammett equation. The kinetics are in good agreement with the assumption of a primary decomposition into arylnitrene.

Walker and *Waters* [34] also studied the thermal decomposition of phenyl-, *p*-methoxyphenyl-, and cyclohexyl azide in different solvents and confirmed the earlier results. They found that thermal decomposition in cumene gives large amounts of dicumyl, formed as a result of hydrogen abstraction by *p*-methoxyphenylnitrene. These workers postulated that the formation of azoaryls occurs via ArNH radicals which combine together to give hydroazaryls; these are then dehydrogenated by other arylnitrenes to give azoaryls and, new ArNH radicals.

In hydrocarbons containing double bonds capable of undergoing addition such as styrene or indene, triazoles or

[38] *P. A. S. Smith* and *B. B. Brown*, J. Amer. chem. Soc. *73*, 2435 (1951); cf. also the review article by *J. H. Boyer* and *F. C. Canter* [17].

[39] *P. A. S. Smith, B. B. Brown, R. K. Putney*, and *R. F. Reinish*, J. Amer. chem. Soc. *75*, 6335 (1953).

[39a] *J. Meisenheimer, O. Senn*, and *P. Zimmermann*, Ber. dtsch. chem. Ges. *60*, 1736 (1927).

[40a] *R. Huisgen, D. Vossius*, and *M. Appl*, Chem. Ber. *91*, 1 (1958).

[40b] *R. Huisgen* and *M. Appl*, Chem. Ber. *91*, 12 (1958).

[40c] *M. Appl* and *R. Huisgen*, Chem. Ber. *92*, 2961, 2966 (1959).

[41] *K. E. Russell*, J. Amer. chem. Soc. *77*, 3487 (1955).

[42] *T. F. Fagley, J. R. Sutter*, and *R. L. Oglukian*, J. Amer. chem. Soc. *78*, 5567 (1956).

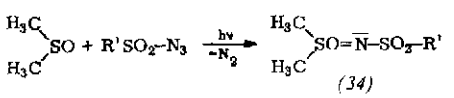
aziridines are preferentially formed. The activation energy for the triazole formation followed by elimination of nitrogen is 15–20 kcal/mole lower than that for nitrene formation.

d) Photolysis and Thermolysis of Acyl Azides to Acylnitrenes and Sulfonylnitrenes

Curtius [33b] already distinguished between two types of acyl azides, *viz.* those capable of undergoing thermal rearrangement and those that are rigid and do not rearrange. Most carboxazides belong to the first group; these also undergo rearrangement on exposure to light [43]. Rigid azides, in addition to the alkyl and aryl azides, include carbamyl azides, azidoformates, and sulfonyl azides.

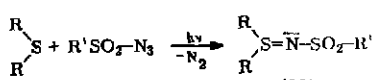
If the cleavage of nitrogen from azides is a monomolecular reaction, then the photolysis and thermolysis of sulfonyl azides [6], as measured by the nitrogen evolved, should be largely independent of the nature of the solvent. This is not true of the photolysis (the penetration of light into the photolysis zone is often impeded by the formation of insoluble irradiation products). On the other hand, the expected independence of the reaction on the type of solvent is observed for the thermal decomposition. Regardless of the residue attached to the sulfonyl group, decomposition of all the sulfonyl azides studied so far starts between 120 and 140 °C; the maximum rate of decomposition occurs between 150 and 180 °C [6]. From this it may be concluded that the primary step in the photolysis and thermolysis of sulfonyl azides is the elimination of elemental nitrogen with formation of free sulfonylnitrenes which are capable of undergoing various reactions, *e.g.* with the solvent.

Dimethyl sulfoxide is an effective co-reactant in the photolytic and thermal formation of sulfonylnitrenes. It gives *N*-sulfonylsulfoximines *(34)* in yields of 20–30 % [6,44].



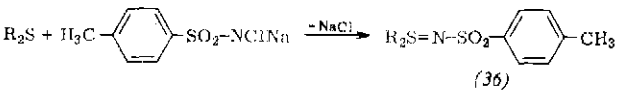
(34)

Thioethers, *e.g.* dimethyl sulfide, can trap [6] the sulfonylnitrene fragments with formation of *N*-sulfonylsulfimines *(35)* [45]. The yields in the reactions studied



(35)

so far are of the order of 50 %, *i.e.* higher than those for *N*-sulfonylsulfoximine formation. Whether nitrenes are involved in the formation of *N*-sulfonylsulfimines, *e.g.* *(35)*, from Chloramine T (*N*-chloro-*p*-toluenesulfonamide) and thioethers [45] is uncertain; this point still requires accurate kinetic analysis. The alternative would be an S_N2 reaction. Cyclic sulfimines *(37)* can be prepared analogously [46].



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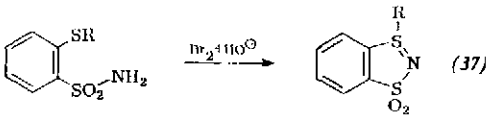
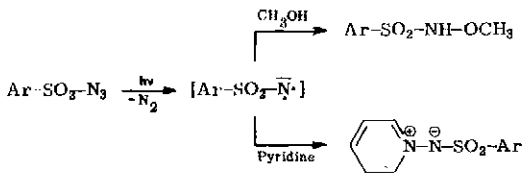


(37)

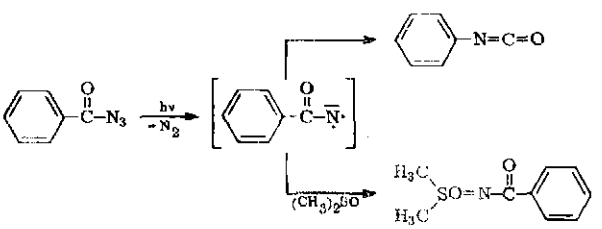
Tertiary phosphines show much higher nucleophilicity and react with acyl azides even in the dark and in the cold [47].

The result of exposure to light of *p*-toluenesulfonyl azide in methanol [6] and pyridine [48] shows that alcohols and amines can undergo nucleophilic reactions with nitrenes (Scheme 3).



Scheme 3. Reaction of sulfonylnitrenes with alcohols and amines.

Contrary to all expectations, photolysis of benzazide in dimethyl sulfoxide yields, in addition to some phenyl isocyanate, mainly sulfoximine *(38)*, the structure of which has been established by synthesis [6]. Thus, it was possible for the first time to capture benzoylnitrene as the primary cleavage product of the Curtius degradation before it rearranged to the isocyanate.



(38)

If the carbonylazido group is located at a tertiary carbon atom *(38a)* and is surrounded by easily accessible C–H bonds, then photolysis yields the expected isocyanate *(38b)*, an approximately equal amount of a mixture of the γ- and δ-lactams *(38c)* and *(38d)*, and the carboxamide *(38e)* [48a,b]. The lactams are formed by an insertion reaction.

[43] *L. Horner, E. Spietschka,* and *A. Gross,* Liebigs Ann. Chem. *573,* 17 (1951).

[44] For preparation of representatives of this class of compounds see [a] *H. R. Bentley* and *J. K. Whitehead,* J. chem. Soc. (London) *1950,* 2081; [b] *H. R. Bentley, E. E. McDermatt,* and *J. K. Whitehead,* Nature (London) *165,* 735 (1950); [c] *F. Misani, F. W. Fair,* and *L. Reiner,* J. Amer. chem. Soc. *73,* 459 (1951).

[45] For preparation of sulfimines see *F. G. Mann* and *W. J. Pope,* J. chem. Soc. (London) *121,* 1052 (1922); *D. S. Tarbell* and *C. Weaver,* J. Amer. chem. Soc. *63,* 2939 (1941).

[46] *A. Wagner,* Angew. Chem. *71,* 386 (1959).

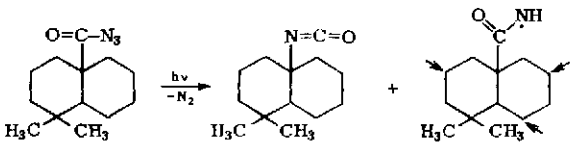
[47] Cf. review article by *L. Horner* and *H. Hoffmann,* Angew. Chem. *68,* 473 (1956).

[48] *G. L. Buchanan* and *R. M. Levine,* J. chem. Soc. (London) *1950,* 2248.

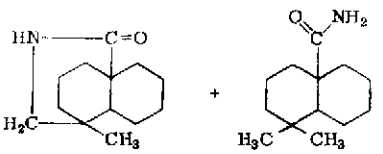
[48a] *W. L. Meyer* and *A. S. Levinson,* Proc. chem. Soc. (London) *1963,* 15.

[48b] Compare also the earlier work of *O. E. Edwards* et al., who were the first to synthetize lactams by photolysis of azides. *J. W. ApSimon* and *O. E. Edwards,* Proc. chem. Soc. (London) *1961,* 461; *J. W. ApSimon* and *O. E. Edwards,* Canad. J. Chem. *40,* 986 (1962); *W. Antkowiak, J. W. ApSimon,* and *O. E. Edwards,* J. org. Chemistry *27,* 1930 (1962).

In formula *(38c)* the arrows denote positions suitable for ring closure with the –NH group.

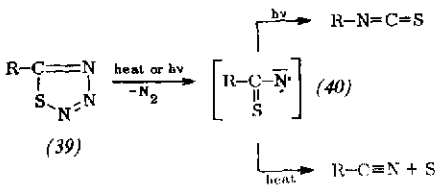


(38a) *(38b)*, 35% *(38c)*, 15%



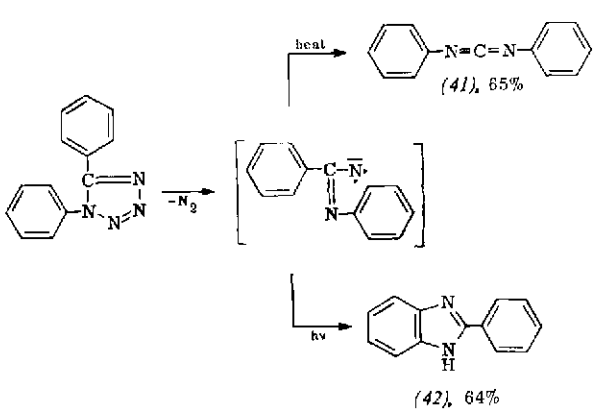
(38d), 10% *(38e)*, 10%

Both thermolysis and photolysis of thiotriazoles *(39)* probably afford thiocarbonylnitrenes *(40)* as a result of loss of nitrogen [49]. Rearrangement of the thiocarbonylnitrene *(40)* to phenyl isothiocyanate, in analogy to the Curtius degradation, occurs in moderate yields only on exposure to light. Thermal decomposition of *(40)* yields a nitrile and sulfur.



(39) *(40)*

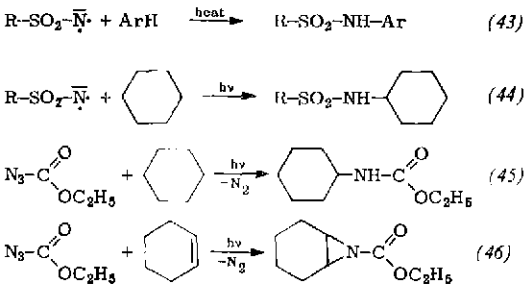
The =N–R analogues of carbonylnitrenes are obtained from tetrazoles by elimination of nitrogen and show a markedly different behavior [1]. On heating, 1,5-diphenyltetrazole undergoes rearrangement to diphenylcarbodiimide *(41)*; on exposure to light, it yields 2-phenylbenzimidazole *(42)* by an insertion reaction without undergoing rearrangement. Insertion reactions occur also



(41), 65% *(42)*, 64%

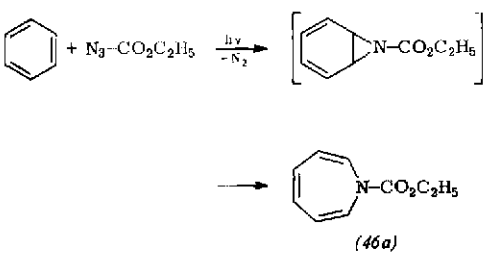
when sulfonyl azides are decomposed thermally in aromatic hydrocarbons *(43)* [50]. This is shown impressively by the decomposition of benzenesulfonyl azide in chlorobenzene in the presence of anthracene. The products are 55 % 1-(benzenesulfonamido)anthracene, 15 % of the 9-isomer and 5–15 % of the 1-isomer. Small amounts of benzenesulfonyl *o*- (or *p*-) chloroanilide are assumed to be formed via an aziridine intermediate analogous to *(46)* [50a]. If t-butyl hydroperoxide is added to a boiling solution of benzenesulfonyl azide in chlorobenzene, the total yield of the *o*-, *m*- and *p*-chloroanilides of benzenesulfonic acid is lower [50b].

Photolysis of sulfonyl azides in cyclohexane affords the corresponding cyclohexylsulfonamide *(44)*. Analogously, on exposure to ultraviolet light (254 mμ) in cyclohexane, ethyl azidoformate loses nitrogen, affording ethyl *N*-cyclohexylcarbamate *(45)* [51] and 3-cyclohexenylurethane [51a] without rearrangement; in cyclohexene, ethyl 2,3-tetramethylenaziridine-1-carboxylate is formed.



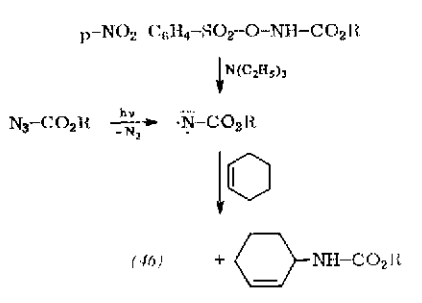
(43) *(44)* *(45)* *(46)*

Analogously the photolysis of ethyl azidoformate in benzene yields *N*-ethoxycarbonylazepine *(46a)* as a stable yellow oil [51b].



(46a)

The alkyl nitrenecarboxylate formed on photolysis of alkyl azidoformate is a rigid nitrene, which preferably adds onto double bonds or is inserted into C–H bonds. Whether the nitrenecarboxylate is formed during the first reaction step or whether the excited azide molecule reacts first with a double or C–H bond and then elimi-



(46) *(46b)*

[49] *W. Kirmse*, Chem. Ber. *93*, 2353 (1960).

[50] *Th. Curtius*, J. prakt. Chem. [2] *125*, 303 (1940).

[50a] *J. F. Tilney-Basset*, J. chem. Soc. (London) *1962*, 2517.

[50b] *J. E. Leffler* and *Y. Tsuno*, J. org. Chemistry *28*, 190 (1963).

[51] *W. Lwowski* and *Th. W. Mattingly*, Tetrahedron Letters *1962*, 277.

[51a] *W. Lwowski, T. J. Maricich*, and *T. W. Mattingly*, J. Amer. chem. Soc. *85*, 1200 (1963).

[51b] *K. Hafner* and *C. König*, Angew. Chem. *75*, 89 (1963); Angew. Chem. internat. Edit. *2*, 96 (1963).

nates N_2 was decided by the following experiment [51a]: alkyl nitrenecarboxylate was produced by photolysis of alkyl azidoformate and by reacting *N*-(*p*-nitrobenzenesulfonoxy)urethane with triethylamine. In both cases cyclohexene was converted to 7-alkoxycarbonyl-7-azabicyclo[4,1,0]heptane *(46)* and 3-cyclohexylurethane *(46b)* in the ratio of 6:1 or 4.5:1, respectively.

With benzene the nitrene-producing system *N*-(*p*-nitrobenzenesulfonoxy)urethane + triethylamine affords *N*-ethoxycarbonylazepine *(46a)* in 50% yield.

3. The Electronic Structure of Nitrenes

Phenyl-, *o*-trifluoromethylphenyl-, benzenesulfonyl-, *p*-toluenesulfonyl-, cyclohexyl-, and styryl azides and ethyl- and phenyl azidoformates were irradiated with ultraviolet light at 77 °K. Electron spin resonance measurements showed that the first four compounds form nitrenes in a triplet state [52]. At the temperature given, the signals maintained their full intensity for more than 18 hours, but disappeared on warming. These measurements prove that the nitrenes derived from the first four azides are biradicals. The nitrenes corresponding to the last four azides obviously undergo further reaction so fast that their stationary concentration is below the limits of detection. The first indication of the biradical nature of nitrenes was the fact that benzenesulfonyl azide promotes polymerization of acrylonitrile at 100–120 °C and that this polymerization is inhibited by *p*-benzoquinone [8, 53].

4. Discussion of Nitrene Formation from Chloramines

The question whether compounds containing the –NHX grouping react in the presence of bases (as halocarbons do in the presence of strong bases to afford carbenes [1]) via nitrenes [Equation (a)] or by an S_N mechanism [Equation (b)] is still unanswered. Path (b) appears to be more likely. The mechanism of the reaction of hydrazoic acid with, for example, sulfuric acid to give hydroxylamine-*O*-sulfonic acid and nitrogen [54] has not been elucidated, either. This reaction is important for an understanding of the degradation of carbonyl compounds with hydrazoic acid in the presence of concentrated sulfuric acid (method of *K. F. Schmidt*) [55]. NH and NH_2^+ have been postulated as possible primary products of this degradation as well as of the Raschig synthesis of hydrazine. According to *Raschig*, chloramine is formed from ammonia and sodium hypochlorite and reacts with alkali affording nitrene NH as the primary product; this then combines with ammonia to give hydrazine, as shown by Equations (c) though (e) [56].

$$NH_3 + NaOCl \rightarrow NaOH + NH_2Cl \quad (c)$$

$$NH_2Cl + NaOH \rightarrow NaCl + H_2O + [NH] \quad (d)$$

$$[NH] + NH_3 \rightarrow H_2N-NH_2 \quad (e)$$

$$[NHCl]^{\ominus} + NH_3 \rightarrow H_2N-NH_2 + Cl^{\ominus} \quad (f)$$

This view has been supported recently by *Audrieth* [57] and, with addition of Equation (f), by *Jander* [58] and *Wannagat* [24]. The increase in the yield of hydrazine with increasing base concentration [57] or on addition of potassamide in liquid ammonia [58] are cited as supporting evidence.

On the other hand, according to the kinetic studies of *Bodenstein* [59], nucleophilic substitution of the chlorine in chloramine by ammonia is supposed to occur in a single, rate-determining step:

$$NH_3 + NH_2Cl \rightarrow (N_2H_5)^{\oplus}Cl^{\ominus} \xrightarrow{HO^{\ominus}} H_2N-NH_2 + Cl^{\ominus} + H_2O$$

Cahn and *Powell* [60] are of the same opinion.

In a kinetic study, *Sisler* [61] showed that the formation of hydrazine in liquid ammonia is a substitution reaction. According to *Yagil* and *Anbar* [62], who studied this reaction under conditions of widely varying base concentration and using methyl-substituted amines and chloramines, the reaction is first order with respect to amine. This, too, points to a nucleophilic attack of the amine on the chloramine or on the chloramide anion. The formation of hydrazinium chlorides [61c] from tertiary amines and chloramine and of *N*-aminopyridinium salts [63] from hydroxylamine-*O*-sulfonic acid and pyridine is interesting from a preparative standpoint, but of no significance for an understanding of the Raschig hydrazine synthesis.

(a) $H_2N-X \xrightarrow[-H_2O]{HO^{\ominus}} [H\bar{N}-X]^{\ominus} \longrightarrow [H\underline{\bar{N}}] + X^{\ominus}$

$[H\underline{\bar{N}}] + :B \longrightarrow H\underline{\overset{\ominus}{N}}-\overset{\oplus}{B}$

(b) $[H\bar{N}-X]^{\ominus} + :B \longrightarrow [B\cdots\bar{N}H\cdots X]^{\ominus} \longrightarrow H\underline{\overset{\ominus}{N}}-\overset{\oplus}{B} + X^{\ominus}$

X = Cl, HSO_4

[52] *G. Smolinsky, E. Wasserman*, and *W. A. Yager*, J. Amer. chem. Soc. *84*, 3220 (1962).

[53] *O. C. Dermer* and *M. T. Edmison*, J. Amer. chem. Soc. *84*, 3220 (1962).

[54] *H. E. M. Specht, A. W. Browne*, and *K. E. Sherk*, J. Amer. chem. Soc. *61*, 1083 (1939).

[55] Cf. *H. Wolff* in: Organic Reactions. Wiley, New York 1949, Vol. III, p. 307.

[56] *F. Raschig* in: Schwefel- und Stickstoffstudien. Verlag Chemie, Berlin 1924, p. 68.

[57] *L. F. Audrieth, E. Colton*, and *M. M. Jones*, J. Amer. chem. Soc. *76*, 1428 (1954); *L. F. Audrieth, U. Scheibler*, and *H. Zimmer*, ibid. *78*, 1852 (1956).

[58] *J. Jander*, Z. anorg. allg. Chem. *280*, 264 (1955).

[59] *M. Bodenstein*, Z. physik. Chem., Abt. A *139*, 397 (1928).

[60] *J. W. Cahn* and *R. E. Powell*, J. Amer. chem. Soc. *76*, 2565 (1954).

[61] *V. F. N. Collier, Jr., H. H. Sisler, J. G. Calvert*, and *F. R. Hurley*, J. Amer. chem. Soc. *81*, 6177 (1959); for previous work on this subject see [61a–c].

[61a] *H. H. Sisler, C. E. Boatman, F. T. Neth, R. Smith, R. W. Shellman*, and *A. D. Kelmers*, J. Amer. chem. Soc. *76*, 3912 (1954).

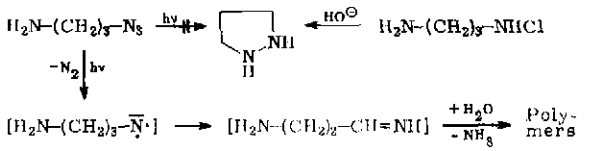
[61b] *R. S. Drago* and *H. Sisler*, J. Amer. chem. Soc. *77*, 3191 (1955).

[61c] *G. M. Omietanski, A. D. Kelmers, R. W. Shellman* and *H. H. Sisler*, J. Amer. chem. Soc. *78*, 3874 (1956).

[62] *G. Yagil* and *M. Anbar*, J. Amer. chem. Soc. *84*, 1797 (1962).

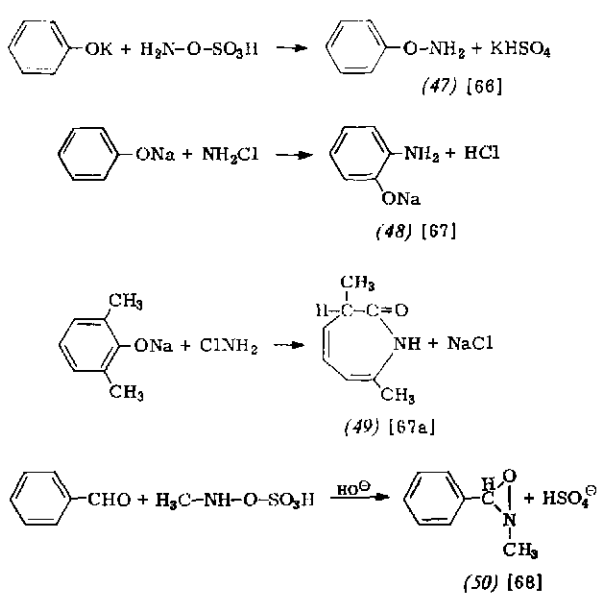
[63] *R. Gösl* and *A. Meuwsen*, Chem. Ber. *92*, 2521 (1959).

A simple method of testing for the alternatives to hydrazine formation is afforded by comparison of two compounds having the azido and chloramino group in corresponding positions. If both compounds react via the nitrene intermediate, then identical results are to be expected, assuming the reaction medium is the same. If different products are obtained, it may be concluded that the reaction paths are different. On reacting 1,3-diaminopropane with sodium hypochlorite, *Lüttringhaus* and co-workers [4] obtained a 30 % yield of pyrazolidine, whereas *Horner* and co-workers did not find pyrazolidine after photolysis of 1-azido-3-aminopropane [64]. Rather, photolysis in benzene yields ammonia and an oxygen-containing polymer, which is perhaps formed according to Scheme 4 [32].



Scheme 4. Photolytic decomposition of 1-azido-3-aminopropane and polymerization of the decomposition product.

Tertiary phosphines and thioethers similar to amines react with hydroxylamine-*O*-sulfonic acid to give phosphinimines and sulfimines, respectively [65]. These reactions too probably occur by nucleophilic substitution of the sulfonyl residue of hydroxylamine-*O*-sulfonic acid and do not involve nitrenes.

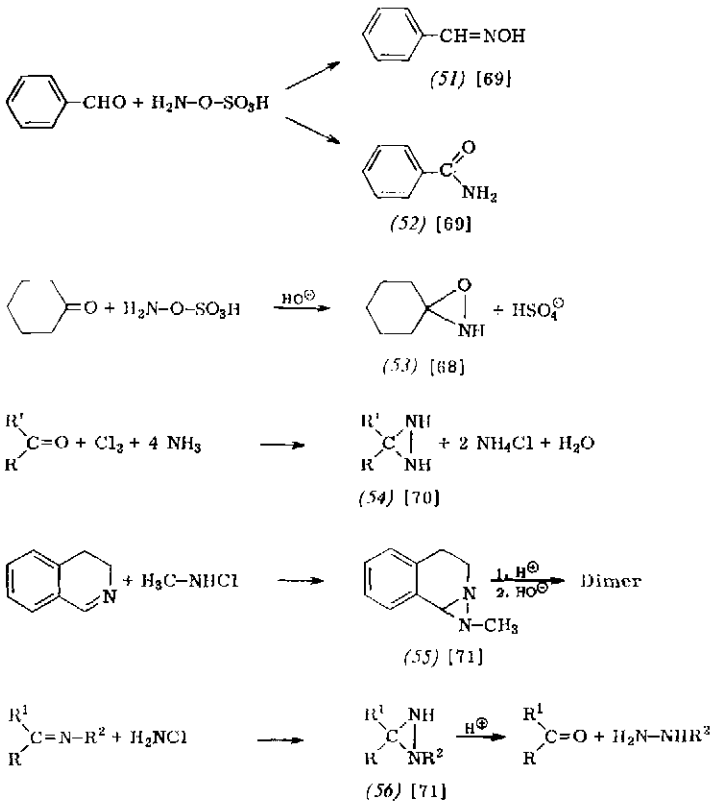


(47) [66]

(48) [67]

(49) [67a]

(50) [68]



(51) [69]

(52) [69]

(53) [68]

(54) [70]

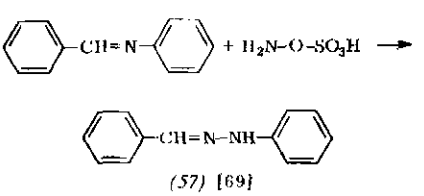
(55) [71]

(56) [71]

Other reactions with chloramine and hydroxylamine-*O*-sulfonic acid, for example *(47)* through *(56)*, probably also involve nucleophilic substitutions.

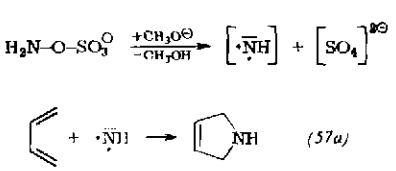
Compound *(50)* is possibly an intermediate in the formation of *(52)*.

Aromatic Schiff bases react with hydroxylamine-*O*-sulfonic acids, probably via a diaziridine intermediate, to give hydrazones *(57)*.



(57) [69]

The formation of pyrroline *(57a)* from butadiene and hydroxylamine-*O*-sulfonic acid in methanol in the presence of sodium ethoxide is interpreted as a 1,4-addition of the nitrene [71a]. However, neither has the reaction mechanism been clarified nor seems this reaction preparatively promising.



(57a)

[64] Confirmed by *A. Lüttringhaus*; personal communication.

[65] *R. Appel, W. Büchner,* and *E. Guth,* Liebigs Ann. Chem. *618,* 53 (1958); *R. Appel* and *A. Hauss,* Angew. Chem. *71,* 626 (1959); Chem. Ber. *93,* 405 (1960); *R. Appel* and *W. Büchner,* Angew. Chem. *71,* 701 (1959); *R. Appel,* ibid. *71,* 374 (1959).

[66] *C. L. Bumgardner* and *R. L. Lilly,* Chem. and Ind. *1962,* 559.

[67] *W. Theilacker,* Angew. Chem. *72,* 498 (1960).

[67a] *W. Theilacker, K. Ebke, L. Seidl,* and *S. Schwerin,* Angew. Chem. *75,* 208 (1963); Angew. Chem. internat. Edit. *2,* 154 (1963).

[68] *E. Schmitz, R. Ohme,* and *D. Murawski,* Angew. Chem. *73,* 708 (1961).

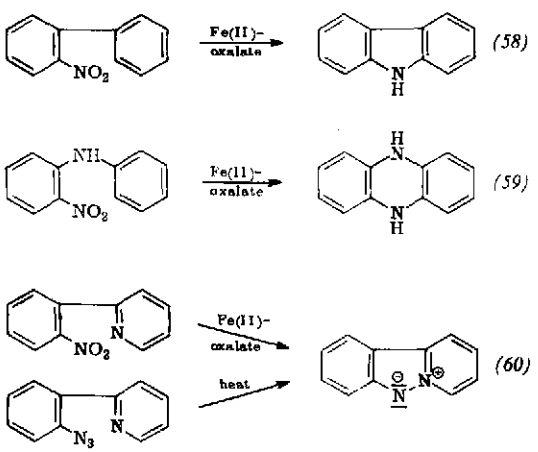
[69] *A. Christmann,* Ph. D. Thesis, Universität Mainz, 1961.

[70] *H. J. Abendroth* and *G. Henrich,* Angew. Chem. *71,* 283 (1959); German printed patent application (June 9th, 1960/March 17th, 1958); *S. R. Paulsen* and *G. Huck,* Chem. Ber. *94,* 968 (1961); Belg. Pat. 588352.

[71] *E. Schmitz,* Angew. Chem. *71,* 127 (1959); *72,* 579 (1960); *73,* 23 (1961); *E. Schmitz* and *D. Habisch,* Chem. Ber. *95,* 680 (1962); *E. Schmitz,* ibid. *95,* 688 (1962); *E. Schmitz, R. Ohme,* and *R.-D. Schmidt,* ibid. *95,* 2714 (1962).

[71a] *R. Appel* and *O. Büchner,* Angew. Chem. *74,* 430 (1962); Angew. Chem. internat. Edit. *1,* 332 (1962).

Further preparative and kinetic studies are necessary before it can be decided whether *N*-halogen compounds (R–NHX) react via nitrenes or by a nucleophilic substitution mechanism. The same is true for the conversion with ferrous oxalate at about 300 °C of *o*-nitrobiphenyl [72] or *o*-nitrobiphenylamine [73] into carbazole *(58)* and 9,10-dihydrophenazine *(59)*, respectively, and for the transformation of 2-(*o*-nitrophenyl)pyridine into ammonium nitreniate *(60)*. The latter is also formed on thermal decomposition but not on exposure to ultraviolet radiation of 2-(*o*-azidophenyl)pyridine [74].

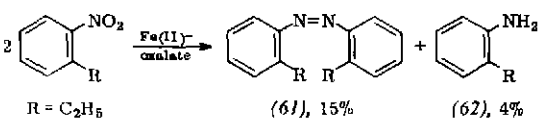


[72] *H. D. Waterman* and *D. L. Vivian*, J. org. Chemistry *14*, 289 (1949).

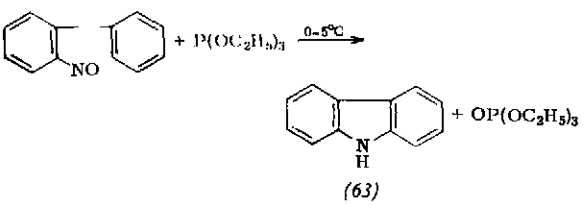
[73] *D. L. Vivian, D. Y. Greenberg*, and *J. L. Hartwell*, J. org. Chemistry *16*, 1 (1951).

[74] *R. A. Abramovitch, Y. Ahmad*, and *D. Newman*, Tetrahedron Letters *1961*, 752.

Both the reactions leading to *(58)* through *(60)* and the conversion of 2-ethylnitrobenzene into *cis*-2,2'-diethylazobenzene *(61)* and *o*-ethylaniline *(62)* take place on the surface of the ferrous oxalate. However, nitrenes and carbenes formed on surfaces differ from the free forms by their lower energy content and by the stereogeometry imposed by the interface. Chemisorbed fragments of the above type should therefore be differentiated from their free forms.



The same reservation applies to the assumption that elimination of oxygen, *e.g.* from *o*-nitrosobiphenyl by triethyl phosphite to give carbazole *(63)*, occurs via nitrenes [75].



We wish to thank the Deutsche Forschungsgemeinschaft for supporting our photochemical investigations.

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[75] *P. J. Bunyan*, and *J. I. Cadogan*, Proc. chem. Soc. (London) *1962*, 78; *J. I. G. Cadogan* and *M. Cameron-Wood*, ibid. *1962*, 361 *P. J. Bunyan* and *J. I. G. Cadogan*, J. chem. Soc. (London) *1963*, 42.

An Acylal of Dimethylketene

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Dedicated to Professor Dr.-Ing. Karl Winnacker on the occasion of his 60th birthday

Free dimethylketene is difficult to handle because of its tendency to dimerize even at low temperatures and to form explosive peroxides with atmospheric oxygen. In contrast, the dimethylketenacylal of dimethylmalonic acid is simple and safe to use. This compound affords dimethylketene on thermal or catalytic cleavage, hence, it can replace the free ketene in nearly all reactions. The synthesis and reactions of this acylal are described.

Introduction

Ketenes were first investigated by *Staudinger*, who synthetized diphenylketene and dimethylketene [1, 2]. The parent compound of this class of substances, ketene [3], was prepared a few years later and became an important industrial chemical. Surprisingly, for a long time dialkylketenes attracted little attention, despite the fact that they are comparable in reactivity to ketene. However, recent publications, particularly on dimethylketene [4–11], indicate renewed interest in these compounds,

[1] *H. Staudinger*, Ber. dtsch. chem. Ges. *38*, 1735 (1905).

[2] *H. Staudinger* and *H. W. Klever*, Ber. dtsch. chem. Ges. *39*, 968 (1906).

[3] *N. T. M. Wilsmore*, J. chem. Soc. (London) *1907*, 91.

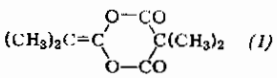
[4] *G. Natta, G. Mazzanti, G. F. Pregaglia, M. Binaghi* and *M. Peraldo*, J. Amer. chem. Soc. *82*, 4742 (1960); Makromolekulare Chem. *44/46*, 537 (1961).

[5] *R. H. Hasek, R. D. Clark* and *J. H. Chaudet*, J. org. Chemistry *27*, 60 (1962).

which nobody had used since *Staudinger*'s classical studies.

Work with dimethylketene is complicated by its great tendency to polymerize. Even at low temperatures, it is readily converted into tetramethyl-1,3-cyclobutanedione. In contrast to ketene, it rapidly forms highly explosive peroxides [12] even with atmospheric oxygen.

Attempts to prepare dimethylketene from dimethylmalonic acid by a simplified procedure gave a stable crystalline compound, shown by our investigations to be the dimethylketenacylal of dimethylmalonic acid *(1)*.



(1)

This compound is simple and safe to handle and can be converted readily into dimethylketene by thermal or catalytic cleavage. In nearly all cases, this acylal can be used in place of free dimethylketene.

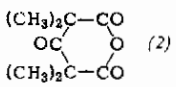
I. Preparation and Elucidation of Structure

Ott [13] and *Staudinger* [14] obtained the polymeric anhydride of dimethylmalonic acid on dissolving dimethylmalonic acid in excess acetic anhydride and evaporating the mixture to dryness *in vacuo*. On heating to about 100 °C, the residue undergoes decomposition to dimethylketene and carbon dioxide.

In a modification of this procedure, we heated dimethylmalonic acid with acetic anhydride to only about 60 °C while continuously removing the resulting acetic acid formed by distillation at 20 mm pressure over a column. The dimethylmalonic acid dissolves rapidly during this process. Surprisingly, when the acetic acid produced (2 moles) is completely removed from the reaction mixture, a rapidly increasing evolution of CO_2 begins, as indicated by a rise in pressure. This evolution continues even when the reaction mixture is brought to normal pressure and allowed to cool; it subsides only after 1 mole of CO_2 is liberated per 2 moles of dimethylmalonic acid. When the excess acetic anhydride is distilled off *in vacuo*, a residue of a crystalline compound is obtained which, after recrystallization from petroleum ether, melts at 80 °C. The yield was about 80 %, based on the dimethylmalonic acid charged.

The pure compound $C_9H_{12}O_4$ which is readily obtainable by this method is thermally quite stable. It can be heated to boiling at atmospheric pressure for a short time without appreciable decomposition. Catalytic amounts of alkaline agents promote rapid decomposition into dimethylketene and carbon dioxide already at about 100 °C. The compound does not react with oxygen under normal conditions; it is quite stable towards atmospheric moisture, so that it can be stored and handled without special precautions.

On heating dimethylmalonic anhydride in a sealed tube in the presence of a trace of trimethylamine, *Staudinger* [14] obtained a compound $C_9H_{12}O_4$ (m.p. 78 °C), to which he assigned the formula of tetramethylacetonedicarboxylic anhydride [2,2,4,4-tetramethyl-3-ketoglutaric anhydride] *(2)*. Comparison of this compound with the



(2)

substance obtained by our method showed that both are identical. This applies to the reactions and to the physical properties.

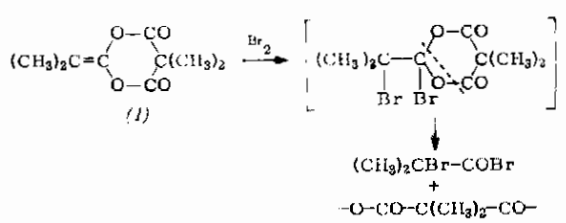
However, some of the reactions we had carried out showed that the compound cannot possess the structure *(2)* assigned to it by *Staudinger*. We concluded that the compound must have the structure of the hitherto unknown acylal *(1)* of dimethylmalonic acid; our conclusion is based particularly on the results presented in the following discussion.

1. Nuclear Magnetic Resonance

The NMR spectrum shows two equally strong signals for methyl groups. This result is in agreement with structure *(1)* but not with structure *(2)*, for which only one signal would be expected for all methyl groups.

2. Action of Bromine

In carbon tetrachloride, the compound adds on one mole of bromine. α-Bromoisobutyryl bromide and polymeric dimethylmalonic anhydride were isolated as the reaction products in nearly theoretical yields. The formation of these products can be readily explained by assigning structure *(1)* to the starting compound:



[6] *G. F. Pregaglia, G. Mazzanti* and *M. Binaghi*, Makromolekulare Chem. *48*, 234 (1961).

[7] *J. L. E. Erickson* and *G. C. Kitchens*, J. org. Chemistry *27*, 460 (1962).

[8] *R. H. Hasek, E. U. Elam, J. C. Martin*, and *R. G. Nations*, J. org. Chemistry *26*, 700 (1961).

[9] *R. H. Hasek, R. D. Clark*, and *J. H. Chaudet*, J. org. Chemistry *26*, 3130 (1961); *R. H. Hasek, E. U. Elam*, and *J. C. Martin*, ibid. *26*, 4340 (1961); *R. H. Hasek, E. U. Elam, J. C. Martin*, and *R. D. Clark*, ibid. *27*, 60 (1962).

[10] *R. G. J. Miller, E. Nield*, and *A. Turner-Jones*, Chem. and Ind. *1962*, 181.

[11] Belg. Pat. 595298 (Sept. 22nd, 1960), Eastman Kodak Co., inventor: *R. H. Hasek* and *E. U. Elam*.

[12] *H. Staudinger:* Die Ketene. F. Enke, Stuttgart 1912; Org. Syntheses *33*, 30 (1953).

[13] *E. Ott*, Liebigs Ann. Chem. *401*, 175 (1913).

[14] *H. Staudinger*, Helv. chim. Acta *8*, 306 (1925).

3. Ozonization

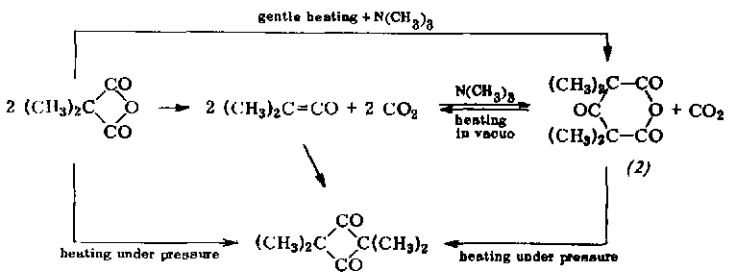
The reaction with ozone in methanolic solution at −78 °C followed by treatment of the primary ozonization product with sodium iodide [15] afforded 0.75 mole of acetone.

4. Hydrogenation

Lithium aluminum hydride induced reductive cleavage of the molecule. One mole of isobutanol and 1 mole of 2,2-dimethyl-1,3-propanediol were isolated.

II. Mechanism of the Formation of the Dimethylketenacylal

Staudinger [14] summarized his findings concerning the cleavage of dimethylmalonic anhydride in the following reaction scheme.



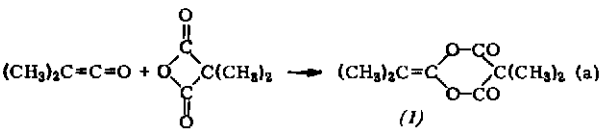
Our observations regarding the preparation of the dimethylketenacylal permit us to throw some light on the question whether the above scheme requires alterations when *(2)* is replaced by the ketenacylal structure *(1)*. Experimental results indicate that two changes should be made:

1. The dimethylketenacylal *(1)* is also formed when trimethylamine is not present as catalyst during the cleavage of dimethylmalonic anhydride. It is merely important that the CO_2 is liberated at low temperatures. The presence of a catalyst is not necessary.

2. It seems unlikely that the dimethylketenacylal *(1)* is formed by recombination of the cleavage products, *viz.* dimethylketene and CO_2, in a 2:1 molar ratio. Attempts to make dimethylketene and CO_2 undergo this reaction have been unsuccessful.

During the preparation of the dimethylketenacylal of dimethylmalonic acid, dimethylketene is formed alongside the carbon dioxide even at room temperature and is partially entrained by the CO_2 stream and lost. If the evolution of CO_2 is allowed to occur *in vacuo*, under otherwise identical conditions, the yield of dimethylketenacylal drops markedly and large amounts of dimethylketene are found in the cold traps. This indicates that free dimethylketene participates in the formation of the acylal.

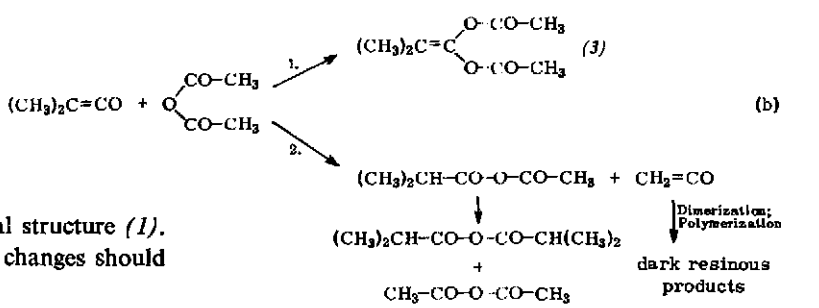
The formation of *(1)* can therefore probably be explained by assuming that the dimethylketene resulting from cleavage of the dimethylmalonic anhydride adds onto unreacted anhydride still present in the system (a).



The assumption that the monomeric, cyclic form of dimethylmalonic anhydride exists in equilibrium with its oligomeric forms in the acetic anhydride solution used in the synthesis is supported by the fact that dialkylmalonic anhydrides have recently been isolated as monomeric compounds [16].

The fact that the dimethylketenacylal of acetic acid *(3)* was obtained as a by-product in the preparation of the dimethylketenacylal of dimethylmalonic acid in acetic anhydride solution at 60–80 °C also lends support to the assumed reaction scheme (a). The formation of this hitherto unknown compound can readily be explained on the basis of addition of acetic anhydride onto dimethylketene (b, 1).

The formation of the dimethylketenacylal of acetic acid *(3)* is hindered by the fact that, particularly above 80 °C,



the competing reaction (b, 2) becomes more and more predominant. Thus, the extremely reactive compound dimethylketene is obviously capable of adding on a proton from the CH_3 groups of the acetic anhydride to its anionic C atom. Ketene is formed and is converted rapidly into dark products, together with the mixed anhydride of isobutyric acid and acetic acid, which on distillation rearranges to the two symmetric anhydrides.

The undesirable side-reaction (b, 2) does not take place when acetic anhydride is replaced by isobutyric anhydride. When the latter is employed as dehydrating agent in our method of preparation of the dimethylketenacylal *(1)*, not the slightest discoloration is ob-

[15] *G. Lohaus*, Ph. D. Thesis, Technische Hochschule Karlsruhe, 1952.

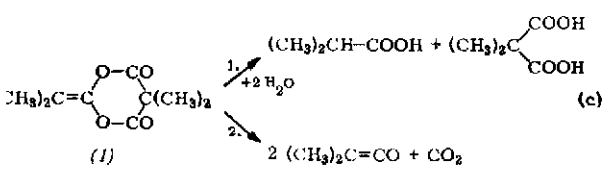
[16] *A. C. Duckworth*, J. org. Chemistry *27*, 3146 (1962).

served during the evolution of the CO_2, the yield of product is greater, and its purity is greater.

A simplified method for the preparation of dimethyl ketene in high yield from dimethylmalonic acid is based on these observations. Dimethylmalonic acid is dehydrated with an excess of isobutyric anhydride at 50–60 °C with continuous removal of the resulting isobutyric acid by vacuum distillation over a fractionating column. At higher temperatures, the anhydride solution readily undergoes cleavage to dimethylketene and CO_2 without forming by-products.

III. Reactions

The dimethylketenacylal of dimethylmalonic acid is relatively stable to hydrolysis. Water has no visible effect on this compound at room temperature. It dissolves only slowly even in boiling water, yielding isobutyric acid and dimethylmalonic acid (Reaction c, 1). Hydrolysis is markedly accelerated by mineral acids or alkali.



We made the surprising observation that alcoholysis, and in many cases also aminolysis, do not proceed in the expected direction. Instead, cleavage of the acylal into dimethylketene and carbon dioxide takes place (Reaction c, 2), and the reaction products are exclusively those of dimethylketene. The course of this reaction indicates that the dimethylketenacylal behaves like dimethylketene itself. It can be used as a starting material for the preparation of dimethylketene, but it can also be used to carry out reactions with nascent dimethylketene (formed in situ).

1. Cleavage into Dimethylketene and Carbon Dioxide

The thermal cleavage of the dimethylketenacylal *(I)* is slow even at its boiling point (about 180 °C). This cleavage is markedly accelerated by addition of small amounts of alkaline agents, best among which are the alkali carbonates. These catalysts permit reduction of the cleavage temperature to 100–150 °C and cause rapid decomposition in this range. The reaction is best carried out by dropwise addition of the molten dimethylketenacylal to a small amount of potassium carbonate contained in a glass vessel which is heated to 150 °C. The rate of addition should correspond to the rate of cleavage desired. The gaseous cleavage product, which constists of 2 parts by volume of dimethylketene and 1 part by volume of carbon dioxide, can be used directly for reactions requiring dimethylketene. If desired, the dimethylketene can be readily isolated in liquid form by partial condensation of the gas stream, the escaping carbon dioxide providing protection from atmospheric oxygen.

In this method, the dimethylketenacylal splits almost without a residue and affords a nearly theoretical yield of dimethylketene. The procedure is safe and permits convenient preparation of large amounts of dimethylketene in the laboratory.

2. Reactions with Alcohols and Phenols

The dimethylketenacylal exhibits remarkable stability toward alcohols and phenols. It can thus be recrystallized without loss from low-boiling alcohols, *e.g.* isopropanol. No alcoholysis to the isobutyric ester and dimethylmalonic monoester was observed. The reaction with alcohols or phenols, like the decomposition of the dimethylketenacylal itself (see Section 1), is markedly accelerated in the presence of alkali carbonates (Figure 1).

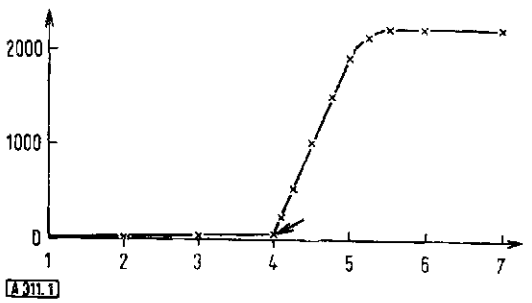
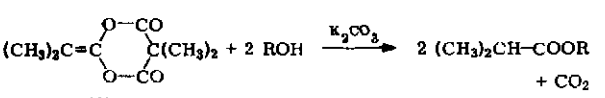


Fig. 1. Kinetics of carbon dioxide liberation in the reaction of the dimethylketenacylal of dimethylmalonic acid with t.-butanol and the effect on same of potassium carbonate (acylal: 0.1 mole; temperature: 83 °C). After 4 hours, 0.1 g of K_2CO_3 was added (arrow on the curve). Ordinate: Quantity of CO_2 evolved [ml]. Abscissa: Reaction time [hours].

The overall reaction can be explained only by assuming that the reaction with the alcohol is preceeded by cleavage of the acylal to dimethylketen. This is indicated by the fact that the acylal remained essentially unaltered after several hours in boiling t-butanol. Only a small fraction, equivalent to the carbon dioxide produced, was found to have been converted into the isobutyric ester. In all the cases studied, the reactions of the acylal with alcohols and phenols proceeded without side reactions, giving the isobutyric ester in nearly theoretical yield (Table 1).

Table 1. Reactions of the dimethylketenacylal of dimethylmalonic acid with alcohols and phenols

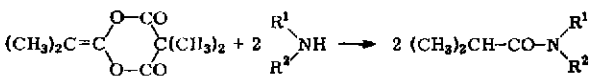


ROH	Molar ratio ROH:*(I)*	Temp. [°C]	$(CH_3)_2CH$–COOR B.p. [°C]	Yield [%]
n-Butanol	4	116	155	95
t-Butanol	2	83	127	95
Cyclohexanol	2.5	150	204	98
Allyl alcohol	2	100	133	92
Ethylene glycol	1	160	132/20 mm	95
2,2-Dimethyl-1,3-propanediol	1	160	238–240	88
Phenol	2	140	103/20 mm	97
Cinnamic alcohol	2	120	117/2 mm	90

3. Reactions with Amines

In contrast to alcohols, amines react vigorously with the dimethylketenacylal *(1)* already at room temperature. The reaction with aniline results in aminolysis and, as already described by *Staudinger* [14], isobutyranilide and dimethylmalonic monoanilide are formed. Butylamine and cyclohexylamine behave similarly. On the other hand, the reaction with secondary amine occurs with

Table 2. Reactions of the dimethylketenacylal of dimethylmalonic acid with amines



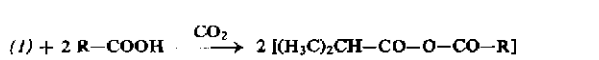
(1)

+ CO_2

R^1R^2NH	Molar ratio R^1R^2NH:*(1)*	Temp. [°C]	$(CH_3)_2CH-CO-NR^1R^2$ B.p. [°C/mm Hg]	Yield [%]
Diethylamine	2	30	110/50	90
Dibutylamine	2	30	123/11	96
Piperidine	2	20	114/15	91
N-Methylaniline	2	80	75/0.2	93

evolution of CO_2 and exclusive formation of isobutyramide. In this case, preliminary decomposition to dimethylketene must again be assumed. The examples of this reaction investigated so far are listed in Table 2.

4. Reactions with Carboxylic Acids



In this reaction too, carbon dioxide is evolved. In the presence of alkali carbonates or alkali salts of carboxylic acids, the reaction occurs readily at 120 °C. It may be assumed that the dimethylketene initially produced reacts first with the carboxylic acid to give the mixed anhydride, which on distillation undergoes disproportionation to isobutyric anhydride and the anhydride of the carboxylic acid used. Since the reagents are used in stoichiometric amounts, and the isobutyric anhydride is readily removed by distillation, this method may offer preparative advantages in the synthesis of carboxylic anhydrides from carboxylic acids.

5. Additions onto Olefins

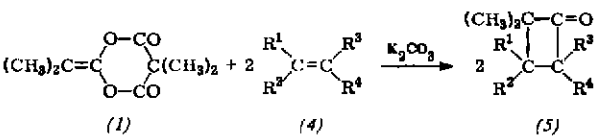
The reaction of dimethylketene with the carbon-carbon double bond has hitherto received little attention. *Staudinger* described the reaction of dimethylketene with vinyl ether and cyclopentadiene [17]. In the case of these relatively reactive compounds, addition takes place with formation of the corresponding 2,2-dimethylcyclobutanone derivatives. Attempts to react styrene with dimethylketene failed and it was assumed [17] that the rates of polymerization for dimethylketene and for styrene are too high compared to the rate of addition.

We have investigated the possibility of adding dimethylketene onto a carbon-carbon double bond to form a cyclic compound. The source of dimethylketene was the dimethylketenacylal of dimethylmolonic acid *(1)*.

Table 3 presents descriptions of reactions with olefins which, in all the cases investigated by us, yielded the anticipated cyclobutanone derivatives.

The reaction is carried out by heating the dimethylketenacylal with the olefin, the latter being preferably used in excess. The addition of catalytic amounts of alkaline substances results in lower reaction temperatures. The reaction with gaseous olefins is carried out

Table 3. Reactions of the dimethylketene acylal with olefins.



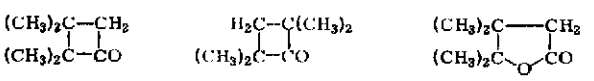
(1) *(4)* *(5)*

+ CO_2

Olefin *(4)*	Molar ratio *(4)*:*(1)*	Product *(5)* Temp. [°C]	B.p. [°C]	Yield [%]	Derivatives
Ethylene	4	140	108	60	2,4-Dinitrophenylhydrazone m.p. 140—141 °C
Propylene	5	130	138	72	2,4-Dinitrophenylhydrazone m.p. 96—98 °C
i-Butylene	6	140	155	70	2,4-Dinitrophenylhydrazone m.p. 116—117 °C
2-Butene	4	140	150	40	Semicarbazone m.p. 186—187 °C
2-Methyl-2-butene	4	130	171	30	Semicarbazone m.p. 184—186 °C
1-Decene	7	120	88/1 mm	67	Semicarbazone m.p. 114—115 °C
Cyclohexene	8	120	68/5 mm	32	Semicarbazone m.p. 216—217 °C (decomp.)
Styrene	2	120	88/1 mm	40	Semicarbazone m.p. 189—191 °C
Butadiene	2	140	91/100 mm	50	Semicarbazone m.p. 188—189 °C

under pressure (preferably in a solvent) in order to increase the olefin concentration and to ensure reaction in a homogeneous phase. The cyclobutanone formed can be isolated by distillation.

The structures of these hitherto unknown cyclobutanone derivatives were elucidated using the product obtained from the reaction of the dimethylketenacylal and isobutylene as an example. The expected product was 2,2,3,3-tetramethylcyclobutanone *(6)*, rather than 2,2,4,4-tetramethylcyclobutanone *(7)*.



(6) *(7)* *(8)*

When the cyclobutanone derivative obtained from the reaction with isobutylene was oxdized with hydrogen peroxide in aqueous potassium hydroxide, the product was a γ-lactone, which proved to be identical with the 3,3,4,4-tetramethylbutyrolactone *(8)* described by *Baumgarten*

[17] *H. Staudinger* and *P. J. Meyer*, Helv. chim. Acta 7, 19 (1924).

[18]. It may be assumed that the other olefins listed in Table 3 also react with the dimethylketene derived from the acylal in the same manner as isobutylene does, *i.e.* that the carbonyl group of dimethylketene adds onto the carbon atom of the double bond which bears the greater number of hydrogens.

IV. Experimental

Preparation of the Dimethylketenacylal of Dimethylmalonic Acid (1)

A mixture of 528 g (4 moles) of dimethylmalonic acid and 1632 g (16 moles) of acetic anhydride is heated slowly to boiling at a pressure of about 10 mm Hg. The acetic acid formed is removed continuously over an efficient fractionating column. The removal of the theoretical amount of acetic acid from the reaction mixture is followed by a spontaneous evolution of CO_2, as indicated by a rise in pressure. The evolution of CO_2 is allowed to continue at atmospheric pressure (vented apparatus) and is complete within a few hours. Removal of the excess acetic anhydride by vacuum distillation affords 300 g (80 %) of a crystalline residue of the dimethylketenacylal; m.p. 80 °C (from petroleum ether).

Reaction of (1) with Alcohols

A mixture of 16 g (0.2 mole) of t-butanol and 18.4 g (0.1 mole) of the dimethylketenacylal *(1)* is refluxed with 100 mg of K_2CO_3 until CO_2 is no longer given off. Distillation of the reaction product affords 27.5 g (75 %) of t-butyl isobutyrate, b.p. 127 °C.

Reaction of (1) with Secondary Amines

Piperidine (42.5 g = 0.5 mole) is added dropwise with stirring to 46 g (0.25 mole) of the dimethylketenacylal *(1)*. The reaction mixture liquefies and CO_2 is evolved. The reaction is complete when no more CO_2 is given off. Distillation affords 72.5 g (91 %) of isobutyric piperidide, b.p. 115 °C/15 mm.

Reaction of (1) with Gaseous Olefins

A 500-ml autoclave equipped with agitator is charged with 92 g (0.5 mole) of the dimethylketenacylal *(1)*, 100 ml of toluene, 500 mg of K_2CO_3, and 210 g of propylene. The mixture is heated slowly to 130 °C. After eight hours, distillation of the contents of the autoclave affords 82 g of 2,2,3-trimethylcyclobutanone (72 % yield based on the dimethylketenacylal); b.p. 138 °C.

Reaction of (1) with Liquid Olefins

A mixture of 9.2 g (0.05 mole) of the dimethylketenacylal *(1)*, 50 g of 1-decene, and 100 mg of potassium carbonate is heated slowly to 130 °C. The carbon dioxide formed is removed through a reflux condenser. The reaction is complete after 6 hours. Distillation of the mixture *in vacuo* affords 14 g of 2,2-dimethyl-3-octylcyclobutanone (67 % yield based on the dimethylketenacylal); b.p. 88 °C/1 mm Hg.

Received, June 4th, 1963 [A 311/109 IE]
German version: Angew. Chem. *75*, 841 (1963)

[18] *H. E. Baumgarten*, J. Amer. chem. Soc. *75*, 979 (1953).

Preparation of Carbon Tetrachloride from Phosgene

BY PROF. DR. O. GLEMSER
IN COLLABORATION WITH DR. J. SCHRÖDER, DR. K. KLEINE-WEISCHEDE, DR. BORIS MEYER, DR. G. PEUSCHEL, R. FLÜGEL, AND DR. D. VELDE

ANORGANISCH-CHEMISCHES INSTITUT DER UNIVERSITÄT GÖTTINGEN (GERMANY)

Dedicated to Prof. Dr. Karl Winnacker on the occasion of his 60th birthday

Carbon tetrachloride can be prepared from phosgene at 300–450 °C. The catalysts for the reaction are transition metals of Groups V to VIII deposited on activated charcoal as carrier. Carbon monoxide and chlorine may be used as starting materials instead of phosgene.

Although at one time carbon tetrachloride was made principally from carbon disulfide and chlorine, by far the largest quantity is now made by chlorination of methane. In the latter process

$$CH_4 + 4\,Cl_2 \rightarrow CCl_4 + 4\,HCl \qquad (1)$$

four moles of hydrogen chloride are formed for each mole of carbon tetrachloride; thus, only half of the chlorine charge is converted into carbon tetrachloride.

For numerous reasons it was desirable to achieve a synthesis of carbon tetrachloride in which no hydrogen chloride is formed or which converts the chlorine quantitatively into carbon tetrachloride. These conditions are met by the decomposition of phosgene into carbon tetrachloride and carbon dioxide:

$$2\,COCl_2 \rightleftarrows CCl_4 + CO_2 \qquad (2)$$

Stock and co-workers [1–3] and *Fink* and *Bonilla* [4] found this reaction to be thermodynamically possible.

[1] *A. Stock* and *W. Wustrow*, Z. anorg. allg. Chem. *147*, 245 (1925).
[2] *A. Stock*, *W. Wustrow*, *H. Lux*, and *H. Ramser*, Z. anorg. allg. Chem. *195*, 140 (1931).
[3] *A. Stock*, *H. Lux*, and *W. Wustrow*, Z. anorg. allg. Chem. *195*, 149 (1931).
[4] *C. G. Fink* and *C. F. Bonilla*, J. physic. Chem. *37*, 1135 (1933).

According to the latter authors, at 400 °C the equilibrium in reaction *(2)* should be displaced to the extent of 70 % in the direction of carbon tetrachloride.

However, neither *Stock* and collaborators nor *Fink* and *Bonilla* were able to achieve a successful experimental process. In the most favorable case, the former group obtained only a trace of carbon tetrachloride on passage of phosgene over activated charcoal at 400 °C. They arrived at the conclusion that the decomposition of phosgene according to *(2)* "cannot take place to any detectable extent" at 400 °C. *Fink* and *Bonilla* obtained the same results both with pure activated carbon and with charcoal impregnated with nickel, copper, cobalt, iron(III), or chromium(III) sulfates.

It was only in 1957 that *Haszeldine* and *Iserson* [5] succeeded in producing carbon tetrachloride via the reaction of phosgene with phosphorus pentachloride over activated charcoal. They heated the reactants in an autoclave for 18.5 hours at 365–375 °C and obtained up to 70 % carbon tetrachloride and $POCl_3$ according to the equation

$$COCl_2 + PCl_5 \rightarrow CCl_4 + POCl_3$$

Kung [6] patented a process in which carbon tetrachloride is formed from phosgene in yields of up to 86 %. The reaction takes place over Friedel-Crafts catalysts such as $AlCl_3$ and $FeCl_3$ at pressures of up to 186 atm.

At the suggestion of Farbwerke HoechstAG [7], the Institut für Anorganische Chemie of the University of Göttingen started work in 1954 on a process for the preparation of carbon tetrachloride from phosgene at atmospheric pressure.

Extensive experimentation showed that activated charcoal impregnated with transition metals of Groups V to VIII of the periodic system, particularly Mo and W, catalyses the decomposition of phosgene to carbon tetrachloride and CO_2. The optimum temperature range lies between 300 and 450 °C.

Apparatus

The experimental apparatus is shown schematically in Figure 1.

The reactor consists of two different quartz tube coils S, each with 12 turns, connected in parallel. The coil axis is 400 mm long and the internal coil diameter is 125 mm. The internal diameter of one spiral tube is 15 mm, and that of the other

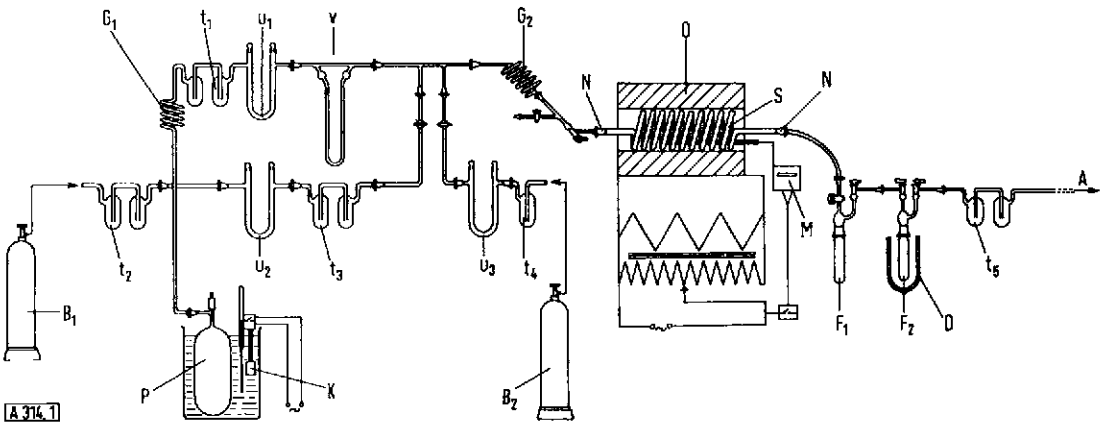


Fig. 1. Apparatus for the preparation of carbon tetrachloride from phosgene. P = Phosgene feed tank (glass); K = immersion thermostat; $B_{1,2}$ = carrier gas cylinders; $t_{1,2}$... = bubble counters; $U_{1,2}$... = drying tubes, V = flowmeters; $G_{1,2}$ = stress-relieving coils; N = standard taper ground joints; O = reactor furnace; S = quartz tube coils; M = temperature controller; $F_{1,2}$ = condensing traps; D = Dewar flask; A = to vent.

20 mm. The phosgene is fed from the feed tank P into the reactor tube via a bubble counter t_1, a drying tube U_1 filled with calcium chloride and phosphorus pentoxide, and a flowmeter V_1. All connections are made with standard taper ground-glass joints. The other end of the reactor is connected to two traps F_1 and F_2 which in turn are connected to the outlet bubble counter t_5. The exit gas is led to the vent. The apparatus is also provided with connections for the introduction of different gases B_1 and B_2 into the reactor. The feed lines for these gases also incorporate drying systems. Coils G_1 and G_2 serve to relieve stresses in the apparatus and to facilitate changing of the reactor coils or phosgene feed tanks. With the exception of the quartz reactor coils, the entire apparatus is made of Jena glass 20. The phosgene is stored in steel cylinders and distilled out as required into the glass bomb P used as feed tank.

The phosgene feed rate can be adjusted during the experiment by means of ground-joint reducing valve at the feed tank. This valve gives adequate flow regulation provided the feed tank is kept at constant temperature. Thus, the latter is suspended in a 20-liter glass vessel filled with water, the temperature of which is controlled by means of an immersion thermostat. The phosgene tank is weighed to ±0.01 g before and after each experiment, and the feed rate can then be calculated from the duration of the reaction.

The reaction products (CCl_4, some CO_2, and unchanged $COCl_2$) collected in the cold traps are carefully hydrolysed with 60 % KOH. Carbon tetrachloride is not attacked by 60 % KOH, while phosgene is converted into potassium chloride (part of which crystallizes in the trap), carbon monoxide, chlorine, and carbon dioxide; this reaction is highly exothermic.

[5] *R. N. Haszeldine* and *H. Iserson*, J. Amer. chem. Soc. *79*, 5801 (1957); Brit. Pat. 855785 (Feb. 7th, 1957).

[6] *F. E. Kung*, German published patent application 1048896; U.S.-Pat. 2892875 (Nov. 15th, 1956).

[7] German Patent 1092895 (Apr. 2nd, 1957), inventors: *O. Glemser*, *G. Peuschel*, and *R. Flügel*; German Patent 1112727 (Aug. 1st, 1959), inventor: *O. Glemser*.

After hydrolysis, the carbon tetrachloride is separated from the aqueous phase, washed with potassium hydroxyde to remove traces of phosgene, and finally distilled. The distillate is dried over calcium chloride and weighed. Infrared analysis showed that a single distillation from aqueous potassium hydroxide and drying over calcium chloride suffice to give a product which is purer than commercial technical grade carbon tetrachloride. Hexachloroethane could not be detected in significant amounts.

The catalyst may be prepared by direct vaporization of the chlorides of the transition metals of Groups V to VIII onto the activated carbon. Alternatively, the carbon can be impregnated with solutions of salts of the transition metals, dried, reduced with hydrogen, and finally chlorinated (preferably at room temperature) with phosgene or chlorine.

With tungsten hexachloride on Katepon F 12 (Degussa's activated carbon) the conversion of phosgene into carbon tetrachloride was 60 % at a phosgene feed rate of 0.93 liter/h and a temperature of 500 °C. With a mixed $MoCl_5$ and WCl_6 catalyst on Katepon F 12 at 400 °C, we made the surprising observation that the performance of the catalyst is actually improved despite a decrease in the phosgene conversion. Here the performance is judged by the grams of CCl_4 formed per gram of catalyst per hour (cf. Figure 2).

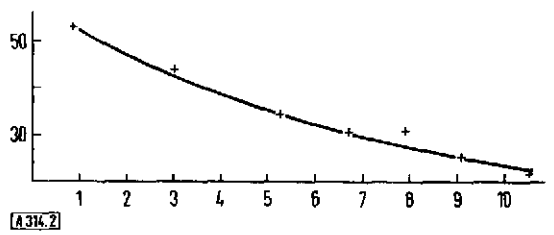


Fig. 2. Conversion of $COCl_2$ and CCl_4 at 400 °C with increasing feed rate. Catalyst: $MoCl_5$ + WCl_6 on Katepon F 12.
Ordinate: Conversion to CCl_4 [%].
Abscissa: Feed rate of $COCl_2$ [l/h].

As can be seen from the graph, even at a feed rate of 10 liters of phosgene per hour the conversion is still 24 %. Longer contact times, achieved by increasing the catalyst volume, increase the conversion of phosgene into carbon tetrachloride further even at high feed rates.

It is interesting to note that the same quantities of ammonium molybdate give different conversions of phosgene into carbon tetrachloride when deposited on different activated carbons, even though the reaction conditions (temperature, catalyst volume, feed rate) remain the same. A linear dependence of the phosgene conversion on the surface areas of the various activated carbon catalyst carriers used (as determined by the iodine adsorption method) was obtained; this is shown in Figure 3.

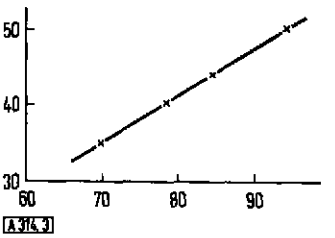


Fig. 3. Conversion of $COCl_2$ into CCl_4 as a function of the surface area of the activated carbon.
Ordinate: Conversion into CCl_4 [%].
Abscissa: Iodine adsorption [%].

It is assumed that the formation of carbon tetrachloride from phosgene proceeds via the steps outlined below, although it remains uncertain whether radical reactions are involved.

$$COCl_2 \rightarrow COCl^+ + Cl^-$$
$$MoCl_5 + Cl^- \rightarrow MoCl_6^-$$
$$COCl^+ + MoCl_6^- \rightarrow CCl_4 + MoOCl_3$$
$$MoOCl_3 + COCl_2 \rightarrow CO_2 + MoCl_5$$

A further advantage of the process is that carbon monoxide and chlorine may be used as starting materials in place of phosgene.

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German version: Angew. Chem. 75, 823 (1963)

COMMUNICATIONS

Separation and Determination of Inorganic Ions in Glacial Acetic Acid [1]

By Dr. B. Sansoni and Dipl.-Chem. R. Stolz

Chemisches Institut der Universität Marburg/Lahn (Germany)

The use of non-aqueous solvents permits numerous novel separations of inorganic ions by precipitation [2]. We have now developed a qualitative scheme for separating cations in solution in glacial acetic acid [3]. Metal acetates containing water of crystallization were dried for 15 hours over P_2O_5; technically pure glacial acetic acid was recrystallized once.

Separation Scheme [2a, 3]

Cations present: Ag, Tl, Bi, Pb, Cu, Cd, Cr, Al, Ni, Zn, Ba, Sr, Mg, NH_4
Insoluble: Cr, Al

Pptd. by KSCN: Ag, Tl, Pb, Cu, Cd, Ni
Pptd. by H_2SO_4: Bi, Zn, Ba, Sr, Mg, NH_4
Pptd. by $SCN^{\ominus}$, dissolved in water: Ag, Cu, Tl, Pb/Cd, Ni (Cu)
Pptd. by H_2SO_4, dissolved in dil. HNO_3: Ba, Sr/Bi, Zn, Mg, NH_4

Metal ions which fall into a single group in aqueous qualitative analysis often fall into different precipitation groups in non-aqueous media. The precipitates are often soluble in water. According to the results of conductometric titrations, the following precipitates are obtained in glacial acetic acid: AgSCN, TlSCN, $Pb(SCN)_2$, $Cu(SCN)_{1.4}$ [a $CuSCN/Cu(SCN)_2$ mixture], $Cd(SCN)_2$, $Ni(SCN)_2$; $Bi_2(SO_4)_3$, $BaSO_4$, $SrSO_4$, $MgSO_4$, $(NH_4)_2SO_4$. With $SCN^{\ominus}$ $HgAc_2$ first gives $Hg(SCN)_2$, then $Hg(SCN)_3^{\ominus}$ and finally, $Hg(SCN)_4^{2-}$.

The electrical conductivities and dielectric constants of solutions of the pure acetates in glacial acetic acid were measured under analytical conditions, *viz.* acetic acid,

analytical grade, containing 0.1–0.3 % H_2O; acetates treated as above; solutions containing 0.2–0.9 % H_2O; 25 ± 0.2 °C; measurements made in a glove-box over P_2O_5 [3]. The specific conductivity of glacial acetic acid was 1.0×10^{-7}–1.1×10^{-7}, of 0.1 M acetate solutions 1×10^{-5}–2×10^{-5} (NH_4, Ba), 8.7×10^{-6}–7.7×10^{-6} (Sr, Mg, Tl), 1.1×10^{-6}–2.2×10^{-6} (Ni, Cd, Pb) and 0.9×10^{-7}–1.1×10^{-7} (Bi, Cu; 0.01 M) [mho/cm]. The minimum equivalent conductivity occurs between 0.1 and 0.01 M and decreases in the order NH_4, Tl; Ba, Sr, Mg; Cd, Ni, Pb from 0.30 to 0.005, and for Cu and Bi to < 0.005 [mho·cm²/Val]. The dielectric constants of 0.1 M solutions were from 7.3 to 8.2, and of 0.01 M solutions from 6.5 to 6.7. These figures are remarkably close to the dielectric constant of the solvent employed, *i.e.* from 6.4 to 6.5 (water-free 6.14).

Thus, the metal acetates are only weakly ionized in glacial acetic acid. This, together with solvation differences [1b], is a fundamental reason for the different, and unfortunately often less quantitative nature of non-aqueous precipitations in solvents of low dielectricity constant in comparison with those in aqueous medium. Sometimes the precipitation of a cation depends strongly on the nature of the anion, which has the same cause.

From 5 to 120 mg of nitrate can be quantitatively determined by conductometric titration in glacial acetic acid by precipitation with 0.5 N $BaAc_2\cdot H_2O$ as $Ba(NO_3)_2$, and from 20 to 200 mg of sodium can be determined similarly by precipitation with 0.5 N H_2SO_4 or $(COOH)_2\cdot 2H_2O$. Ni^{2+} was separated from Co^{2+} by precipitation with SCN^- as $Ni(SCN)_2$. Deep blue $[Co(SCN)_4]^{2-}$ remains in solutions [4].

Received, March 18th, 1963 [Z 476/303 IE]
Publication withheld until now at the author's request.
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[1] Separations in non-aqueous solution III. [a] Part I, *B. Sansoni*, Angew. Chem. *66*, 595 (1954); [b] Part II, Z. Naturforschg. *11b*, 117 (1956).

[2] [a] *B. Sansoni* and *W. Hass*, Graduation Thesis, Regensburg, March, 1953; [b] Angew. Chem. *66*, 330 (1954); [c] *K. Starke* and *A.T. Casey*, M.S. Thesis, University of Vancouver, B.C. (Canada), April 1953; *H. Hardt*, Lecture at Bonn (Germany) 1962; see Angew. Chem. *74*, 500 (1962).

[3] *R. Stolz*, Ph. D. Thesis, Universität Marburg/Lahn, 1963.

[4] *Sansoni, Arold, Murawski*, and *v. Elsner*, unpublished experiments, 1962/1963.

Experiments with Chloramine T in the Toluenesulfonylurea Series

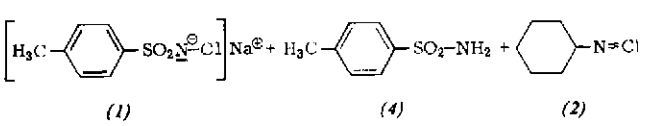
Reactions of Chloramine T with Alkyl Isonitriles

By Dr. W. Aumüller

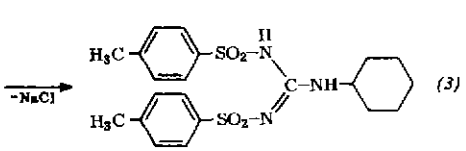
Farbwerke Hoechst AG., vormals Meister Lucius & Brüning Frankfurt/Main (Germany)

Dedicated to Professor Dr. K. Winnacker on the occasion of his 60th birthday

If chloramine T *(1)* is mixed with an isonitrile, *e.g.* cyclohexyl isocyanide *(2)*, and the mixture is warmed on a steam-bath in the presence of $CaCO_3$, it soon decrepitates. The remarkable product formed is 1,2- bis(toluenesulfonyl)-3-cyclohexylguanidin *(3)*. We have obtained *(3)*, m.p. 122 to 124 °C, in 61 % yield from equivalent amounts of chloramine T, *p*-toluenesulfonamide *(4)*, and cyclohexylisonitrile in aqueous acetone as solvent.

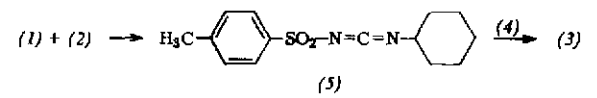


(1) *(4)* *(2)*



(3)

This course of reaction was unexpected in view of the experiments of *Nef* [1] with alkyl isonitriles. It can be interpreted that equivalent amounts of chloramine T and cyclohexylisonitrile react together first to form *(5)*, with subsequent addition of one mole of *p*-toluenesulfonamide.



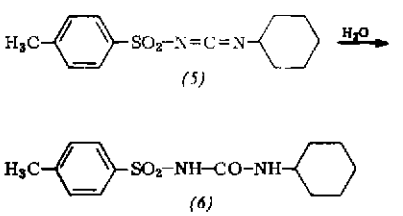
(5)

The reactivity of *N*-(*p*-toluenesulfonyl)-*N'*-alkylcarbodiimide [2] is understandable when it is compared with that of the isocyanates: *p*-toluenesulfonyl isocyanate is considerably more reactive than cyclohexyl isocyanate, for instance.

Although it did prove possible to split off HCl from *N*-(*p*-toluenesulfonyl)-*N'*-cyclohexylchloroformamidine by heating it *in vacuo*, the initial product formed, *viz.* *(5)*, could not be isolated, as it polymerized at once.

It was then obious to try alterations in the conditions of the reaction between equivalent amounts of chloramine T and alkyl isonitriles in order to avoid interaction of the assumed intermediate, *N*-(*p*-toluenesulfonyl)-*N'*-alkylcarbodiimide, with the *p*-toluenesulfonamide which evidently appears as a by-product.

Partial addition of water onto *(5)* was achieved by using great dilutions in aqueous acetone. However, the yields of *(6)*, were very low, and could not be increased, despite variations in the experimental conditions.

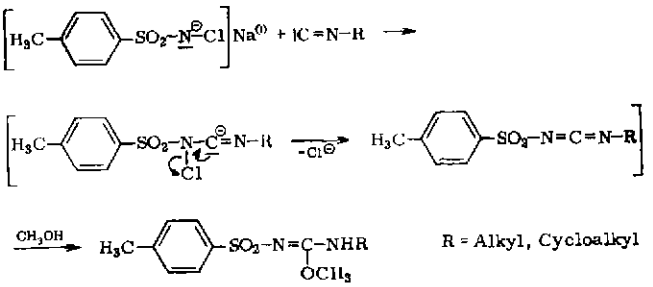


(5)

(6)

However, chloramine T reacts smoothly and clearly with isonitriles if methanol or ethanol is used as solvent. The alcohol adds on preferentially to the assumed intermediate. With cycloalkyl isonitriles, up to 65 % *N*-(*p*-toluenesulfonyl)-*N'*-cycloalkylisourea ethers are obtained by elimination of NaCl. Hydrolysis of these ethers gives *N*-(*p*-toluenesulfonyl)-*N'*-cycloalkylureas in nearly quantitative yield. Aliphatic isonitriles give lower yields of isourea ethers.

We propose the following tentative course of reaction for the formation of the *N*-(*p*-toluenesulfonyl)isourea ethers:



R = Alkyl, Cycloalkyl

Received, June 4th, 1963 [Z 549/380 IE]
German version: Angew. Chem. 75, 857 (1963)

[1] *I. U. Nef*, Liebigs Ann. Chem. *270*, 267 (1892); *280*, 291 (1894).

[2] To our knowledge, no representative of this type of compound has yet been isolated.

Some New Reactions of Sodium Bistrimethylsilylamide

By Dr. C. R. Krüger and E. G. Rochow

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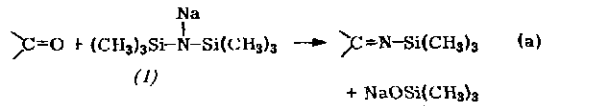
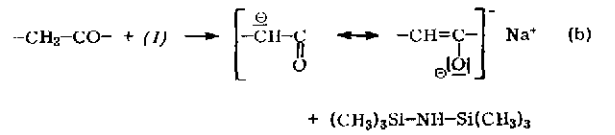
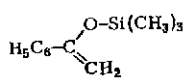
Although sodium bistrimethylsilylamide *(1)* reacts with non-enolizable carbonyl compounds according to Equation *(a)* [1],



carbonyl compounds with reactive hydrogen are converted almost quantitatively into the corresponding sodium enolates (Equation *(b)*):

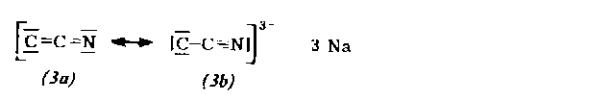


Compound *(1)* is therefore useful as a base even for sterically hindered condensation reactions (ethyl isobutyrate → 30 % ethyl isobutyrylisobutyrate). Numerous sodium enolates react with halogenosilanes to form *O*-silyl-substituted enols, *e.g. (2)*, b.p. 93–94/14 mm, $n_D^{23} = 1.5008$.



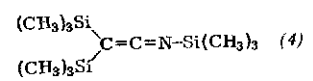
(2)

Compound *(1)* also reacts with reactive nitriles in analogy to Equation *(b)*. Acetonitrile gives a quantitative yield at −60 to +30 °C of an ether-insoluble salt *(3)* that is isosteric with isocyanates and cyanamides.



(3a) *(3b)*

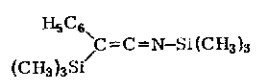
The limiting form *(3b)* reacts with methyl iodide to form pivalonitrile, while *(3a)* reacts with trimethylchlorosilane to yield the surprisingly stable 1-bistrimethylsilyl-3-trimethylsilylketenimine *(4)* (b.p. 214–216 °C, $n_D^{20} = 1.4560$, $d^{23} =$



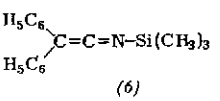
(4)

0.8269; νC=C=N: 2020 cm^{-1}; the proton magnetic resonance spectrum shows two signals of the $Si(CH_3)_3$-groups at δ = 0.20 ppm and δ = 0.098 ppm in a ratio of 1:2).

In the same way, mono- and diphenylacetonitrile gave *(5)* and *(6)* as yellow oils.



(5)



(6)

Variation of the reaction conditions leads to condensation of nitriles. Suberodinitrile and *(1)* react in a molar ratio of 1:1 in ether at room temperature to yield 96 % α-cyanocycloheptanonimide (m.p. 97 °C) [2]. Furthermore, *(1)* is useful as a base in Wittig reactions (benzophenone → 92 % 1,1-diphenylethylene).

Received, July 9th, 1963 [Z 541/372 IE]
German version: Angew. Chem. *75*, 793 (1963)

[1] *C. Krüger, E. G. Rochow,* and *U. Wannagat,* Chem. Ber., in the press.

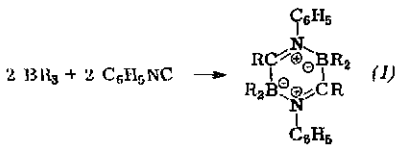
[2] *K. Ziegler* and *R. Aurnhammer,* Liebigs Ann. Chem. *513*, 57 (1934).

Reaction of Boron Alkyls with Isonitriles

By Prof. Dr. G. Hesse and Dipl.-Chem. H. Witte

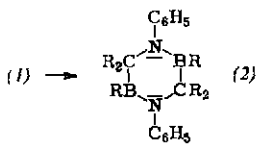
Institut für Organische Chemie der Universität Erlangen-Nürnberg (Germany)

Phenyl isonitrile reacts with trialkylboron compounds in ether at room temperature to yield a new boron-nitrogen heterocycle, *viz.* 2,5-diboradihydropyrazine *(1)*.



(1a): R = C_2H_5, m.p. 144 °C, 39 % yield
(1b): R = n-C_4H_9, m.p. 125 °C, 58 % yield

The infrared spectra of *(1a)* and *(1b)* both contain intense bands at 1560 cm^{-1} and 1553 cm^{-1}, respectively, attributable to a $>C=\overset{\oplus}{N}<$ bond [1]. The structures also agree with the NMR spectra [2]. Compound *(1)* rearranges rapidly above 200 °C into a 2,5-diborapiperazine *(2)*.



(2a): R = C_2H_5, m.p. 204 °C, sublimes
(2b): R = n-C_4H_9, m.p. 186–169 °C (in a sealed tube), sublimes.

On heating with CrO_3 in glacial acetic acid, *(2)* yields di-n-butyl ketone, and on degradation with periodic acid in glacial acetic acid, n-butyl acetate. The infrared spectra of *(2a)* and *(2b)* include a strong peak at 1400 cm^{-1}, which may be due to a BN vibration with partial double bond character [3]. Compounds *(1a)*, *(1b)*, *(2a)*, and *(2b)* are stable crystalline substances that are slightly soluble in water, glacial acetic acid, methanol, or acetone, but readily soluble in non-polar solvents. They are unaffected by boiling aqueous acids and alkalis. Solutions of *(1a)* and *(1b)* in light petroleum rapidly become intense violet on addition of anhydrous $AlCl_3$; *(2a)* and *(2b)* give a weak green color on prolonged standing. Cyclohexyl isonitrile reacts with boron alkyls in the same way as phenyl isonitrile.

Received, July 10th, 1963 [Z 542/373 IE]
German version: Angew. Chem. *75*, 791 (1963)

[1] *J. D. S. Goulden*, J. chem. Soc. (London) *1953*, 997.

[2] We wish to thank *A. Mannschreck*, Heidelberg, for measuring and interpreting these spectra.

[3] *G. M. Wyman, K. Niedenzu,* and *J. W. Dawson*, J. chem. Soc (London) *1962*, 4068.

The Heats of Combustion and Enthalpies of Formation of SiH_4, Si_2H_6, Si_3H_8, and n-Si_4H_{10}

By Prof. Dr. F. Fehér, Dr. G. Jansen, and Dipl.-Chem. H. Rohmer

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We have investigated the enthalpies of formation of silanes. Hitherto only widely varying data [1,2] for monosilane and a single result for disilane [2] were available. We therefore decided to redetermine the enthalpies of formation from heats of combustion by a novel method using the technique according to *Fehér, Kuhlbörsch,* and *Luhleich* [3] for preparing and handling pure SiH_4, Si_2H_6, Si_3H_8, and n-Si_4H_{10}

(free from isotetrasilane). Results of determinations with isotetrasilane will be published later. Combustion in a calorimetric bomb is suitable for disilane, which is readily condensed, and for tri- and tetrasilanes, which are liquids [4]. On account of its low b.p. (−111.6 °C), however, SiH_4 could only be burnt at constant pressure in a specially designed combustion chamber [5]. This method was also applied to disilane.

Table 1 shows the heats of combustion (W_p) at 20 °C and the enthalpies of formation (W_B) derived therefrom for silanes at 20 °C.

Table 1. Heats of combustion (W_p) and enthalpies of formation (W_B) of silanes at 20 °C

Silane	W_p [kcal/mole]	State of aggregation	W_B [kcal/mole]	State of aggregation
SiH_4	−325.2 ± 1.2	g	−11.3	g
Si_2H_6	−575.3 ± 0.5	liq	−36.2	g
Si_3H_8	−835.1 ± 0.7	liq	−54.4	liq
n-Si_4H_{10}	−1092.4	liq	−70.8	liq

The reaction in the bomb yielded α-SiO_2, that in the combustion chamber gave amorphous SiO_2. The difference in enthalpy of these two forms of SiO_2 is important for the calculation of the enthalpy of formation of SiH_4 and was estimated by combustion of disilane in the calorimetric bomb (W_p = −575.3 kcal/mole) and in the combustion chamber (W_p = −568.9 kcal/mole) allowing for the heat of evaporation (5.0 kcal/mole); the value obtained was −5.7 kcal/mole.

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[1] *M. J. Ogier*, Ann. Chim. Phys. [5] *20*, 25, 37 (1880); *H. von Wartenberg*, Z. anorg. allg. Chem. *79*, 71 (1913); *E. O. Brimm* and *H. M. Humphreys*, J. physic. Chem. *61*, 829 (1957).

[2] *S. R. Gunn* and *L. G. Green*, J. physic. Chem. *65*, 779 (1961).

[3] *F. Fehér*, *G. Kuhlbörsch*, and *H. Luhleich*, Z. anorg. allg. Chem. *303*, 294 (1960).

[4] *G. Jansen*, Ph. D. Thesis, Universität Köln, 1960.

[5] *H. Rohmer*, Diploma Thesis, Universität Köln, 1963.

New Stereospecific Catalysts for Polymerizing Butadiene

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We have found new stereospecific catalysts for polymerizing butadiene which do not rely on organometal compounds of Group I to III metals.

When a mixture of molybdenum pentachloride and cobalt carbonyl was used as a catalyst, butadiene was polymerized to a completely amorphous polymer which has a 1,2-content (determined by the infrared analysis according to Morero [1]) of 99 % without fractionation. All operations were carried out under nitrogen. A typical polymerization procedure is as follows: A solution in benzene of dicobalt octacarbonyl (0.25 mmole, 0.5 matom as Co) was added to a suspension of molybdenum pentachloride (0.5 mmole) in benzene. The resulting slurry contained a black precipitate and was heated at 50 °C for one hour, about 19 mole-% of carbon monoxide being evolved. Polymerization of butadiene was effected by this aged catalyst mixture at 40 °C for 18 hours; yield: 60 %. The intrinsic viscosity [η] of the polymer lay in the range 2–3, depending upon the conditions of polymerization. Polymer with [η] greater than 2 is a rubber-like solid which is soluble in acetone and ether and very soluble in benzene giving a highly viscous solution.

The X-ray diffraction pattern showed complete absence of crystallinity in the polymer. Catalytic hydrogenation of the polymer ([η] = 2.5) using $Pd/CaCO_3$ [2] was carried out at room temperature in benzene. Hydrogen absorption ceased at only 65 % of theoretical amount.

Determination of the degree of unsaturation by the iodine chloride addition method [3] showed that 85 % of the vinyl group reacted.

When the $MoCl_5$ was combined with $Ni(CO)_4$, the polymer obtained with the resultant catalyst was found unexpectedly to be more than 85 % *cis*-1,4-polybutadiene.

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German version: Angew. Chem. 75, 858 (1963).

[1] *D. Morero*, *S. Santambrogio*, *L. Porri*, and *F. Clampelli*, Chim. e Ind. *41*, 756 (1959).

[2] *A. I. Yakubchik* and *G. N. Gromova*, Rubber Chem. Technol. *31*, 156 (1958).

[3] *T. S. Lee*, *I. M. Kolthoff*, and *M. A. Mairs*, J. Polymer Sci. *3*, 66 (1948).

1,3-Dithiolane-2-thione-4,5-dione

By Dipl.-Chem. B. Krebs and Doz. Dr. G. Gattow

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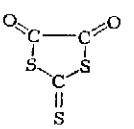
Dedicated to Prof. Dr. Brockmann on the occasion of his 60th birthday

Interaction of equimolar quantities of $SC(SH)_2$ [1] and oxalyl chloride has given rise to 1,3-dithiolane-2-thione-4,5-dione *(1)* for the first time and in quantitative yield as beautifully cristalline wine-red needles.



(1)

A dilute solution of $(COCl)_2$ in $CHCl_3$ is dropped slowly at 0 °C with exclusion of moisture into a solution of $SC(SH)_2$ in $CHCl_3$, when *(1)* is formed smoothly with immediate evolution of HCl. The reaction is completed by heating for 10 minutes at 50 °C. After removal of the $CHCl_3$, *(1)* is recrystallized from n-hexane (m.p. 66 °C, b.p. 90 °C/2 mm; d_4^{25} = 1.890). When heated at atmospheric pressure under nitrogen, *(1)* decomposes above 100 °C into CO_2, CO, COS, and CS_2. It is readily soluble in $CHCl_3$, CCl_4, benzene, ether, but only sparingly soluble in paraffins; it is readily decomposed by polar solvents such as methanol or ethanol. Hydrolysis in water affords oxalic acid and trithiocarbonic acid (→ H_2S + CS_2), together with yellow polymerisation products. This hydrolytic decomposition is also complete within several hours on exposure of *(1)* to a moist atmosphere.

The visible spectrum (solvent: CCl_4, n-hexane) contains a weak R-double band with maxima at 522 and 540 mμ, together with a strong K-band at 417 mμ. The infrared spectrum (in CCl_4 and Nujol) has peaks at 1716 and 1724 (incompletely resolved, s), 1105 (s), 1000 (s), 958 (m), 800 (w), 526 (m), and 468 (w) cm^{-1}.

X-ray diffraction studies (rotating crystal, Weissenberg equator and Weissenberg equi-inclination photographs with Cu-Kα-radiation) about [010] and precession measurements (μ = 30°, Mo-K_α-radiation) about [100] and [001] show that *(1)* crystallizes monoclinically with z = 8 in the space group C_{2h}^4 – P 2/b or C_{2h}^5 – P 2_1/b; a = 11.34 ± 0.02, b = 5.220 ± 0.01, and c = 19.39 ± 0.03 Å; β = 96°50′ ± 30′. X-ray density: 1.886.

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German version: Angew. Chem. 75, 978 (1963)

[1] *G. Gattow* and *B. Krebs*, Z. anorg. allg. Chem. *321*, 143 (1963).

Acid Catalysis of a Wittig Reaction

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Two investigations of the kinetics of the reaction of triphenylalkoxycarbonyl methylene phosphoranes *(1)* with substituted benzaldehydes [1,2] prompt us to report on some of our own results.

Ultraviolet spectroscopic measurements of the rate of reaction of *(1)*, R=C_2H_5,

$(C_6H_5)_3\overset{\oplus}{P}-\overset{\ominus}{C}H-CO_2R$ *(1)*

with benzaldehyde [3] in benzene indicated a reaction of the second order until 60–80 % of *(1)* had reacted; however, it was only when the aldehyde was of extreme purity and when the reaction was carried out under highly purified nitrogen that reproducible results for the rate constants were obtained ($k_2 = 2.6\times10^{-3}$ l/mole/sec at 20 °C). Traces of benzoic acid increased the rate of reaction significantly. This general acid catalysis permits reaction of *(1)*, R=C_2H_5, with ketones, which otherwise do not react [4] or only under severe conditions [5]. Table 1 gives some examples. All the substituted acrylic esters were also made on a preparative scale. Unsymmetric ketones gave mixtures of *cis*- and *trans*-esters; the relative amounts of each were substantially independent of the acid catalysis. Only cyclic ketones and methyl ketones give high yields, probably owing to a steric effect.

Table 1. Yields of β,β-dialkylacrylic esters from 1.3 mole/l of *(1)*, R=C_2H_5, and 6.3 mole/l of ketone in benzene with and without 0.27 mole/l of benzoic acid.

Ketone	Time [a] [h]	Yield [%] without	Yield [%] with acid
Acetone	7	6	80
Methyl ethyl ketone	22	5	89
Methyl n-propyl ketone	25	12	83
Cyclopentanone	21	9	66
Cyclohexanone	4	95	95
Diethyl ketone	22	2	26

[a] At the times given, gas chromatographic analysis indicated that the yields were at a maximum.

In the reaction of *(1)* with acetone, the catalytic effect of *p*-nitrobenzoic acid, *p*-methoxybenzoic acid, acetic acid, or trichloroacetic acid was less than that of benzoic acid.

Protonization of the carbonyl group seems to be the simplest explanation for the acid catalysis. *Wittig* and *Haag* [3] have observed a related acid catalysis during the opening of epoxide rings with triphenylphosphine.

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German version: Angew. Chem. *75*, 858 (1963)

[1] *A. J. Speziale* and *D. E. Bissing*, J. Amer. chem. Soc. *85*, 1888 (1963).

[2] *S. Fliszár* and *R. F. Hudson*, Helv. chim. Acta, in the press; *R. F. Hudson*, personal communication.

[3] *G. Wittig* and *R. Haag*, Chem. Ber. *88*, 1654 (1955); *O. Isler, H. Gutmann, M. Montavon, R. Ruegg, G. Ryser*, and *P. Zeller*, Helv. chim. Acta *40*, 1242 (1957).

[4] *S. Trippett* and *M. D. Walker*, J. chem. Soc. (London) *1961*, 1266; Chem. and Ind. *1961*, 990; *S. Sugasawa* and *H. Matsuo*, Chem. pharmac. Bull. (Japan) *8*, 819 (1960); Chem. Abstr. *55*, 20901a (1961).

[5] *G. Fodor* and *I. Tömösközi*, Tetrahedron Letters (London) *1961*, 579; *H.T. Openshaw* and *N. Whittacker*, Proc. chem. Soc. (London) *1961*, 454.

Complex Fragmentation of β-Amino Aldehydes

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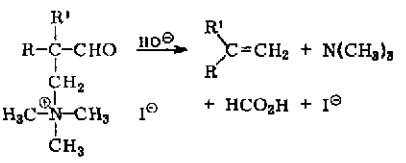
When aldehydes of general formula *(1)* are heated for 1–7 hours with excess (molar proportion 1:10) of 25–33 % NaOH, they readily undergo a complex fragmentation to give the olefin, trimethylamine, and formic acid (yields of up to 98 %).



(1)

	(1a)	*(1b)*	*(1c)*	*(1d)*	*(1e)*
R'	CH_3	CH_3	CH_3	C_2H_5	C_2H_5
R	CH_3	C_6H_5	n-C_3H_7	C_2H_5	n-C_4H_9

The aminoaldehydes *(1)* are readily obtained from the α-branched aldehydes R_2CHCHO by Mannich condensation.

Further work on β-halogenoaldehydes of analogous structure is in progress.

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German version: Angew. Chem. *75*, 791 (1963)

2,2,6,6-Tetramethyl-2,6-disila-4-(β-hydroxyethyl)-1,4-oxathianonium bromide [1]

By Dr. W. Simmler

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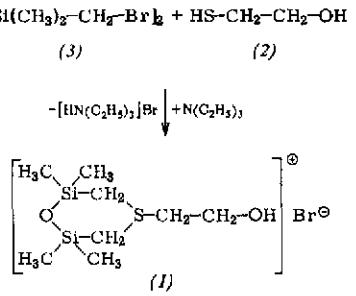
2,2,6,6-Tetramethyl-2,6-disila-4-(β-hydroxyethyl)-1,4-oxathianonium bromide *(1)* has been obtained previously, together with 1,4-dithiane, in a complicated reaction [2] by interaction of bromomethyldimethylchlorosilane and mercaptoethanol *(2)* in the presence of triethylamine as hydrogen-halide acceptor. Compound *(1)* is formed less obscurely in the reaction of equimolar quantities of 1,3-di(bromomethyl)tetramethyldisiloxane *(3)* with *(2)* and triethylamine [3]; however, the practical difficulties are greater because of the NH_4Br precipitated.



(1)

It is noteworthy that *(1)* is also obtainable smoothly in the absence of an HBr acceptor. A solution of *(3)* and *(2)* in the molar proportion 1:4 in an equal weight of ethanol is kept at room temperature for a few days when *(1)* crystallizes out as massive plates. After 10 days, the yield of first crop approaches 58 %; on removal of the ethanol at 30 °C/10 mm,

the mother liquors produce further 16 %. After being washed with cold ethanol and ether, the crystals are analytically pure. The proton magnetic resonance spectrum [4] gave the following data (numbers indicate p.p.m with tetramethylsilane as standard):

$Si(CH_3)_3$	$Si-CH_2-Si$	$S-CH_2-C$	$C-CH_2-O$
0.6	3.0	3.8	4.3

The spectrum was identical with those of specimens prepared according to [2] and [3].

Received, July 25th, 1963 [Z 548/377 IE]
German version: Angew. Chem. 75, 859 (1963)

[1] Part 5 of a series on Functional Silicon Heterocycles; Part 4: *W. Simmler* et al., Chem. Ber. *96*, 1495 (1963).

[2] *W. Simmler*, Chem. Ber. *96*, 349 (1963).

[3] *W. Simmler* and *H. Niederprüm*, German Patent Application, F 37208/IVd/39c (June 30th, 1962) Farbenfabriken Bayer.

[4] Thanks are due to Dr. *H. Walz* for determination of the NMR spectra.

π-Cyclododeca-1,5,9-trienylrhodium(III) Dichloride

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Università di Napoli (Italy)

We have succeeded in preparing the first π-allylic complex of Rh(III), *viz.* π-cyclododeca-1,5,9-trienylrhodium(III) dichloride *(1)*. This complex is obtained in 80 % yield by adding an excess of *trans-trans-trans*-cyclododecatriene *(2)* [1] to a 10 % solution of $RhCl_3$ in ethanol and refluxing the mixture for about 3 hours.

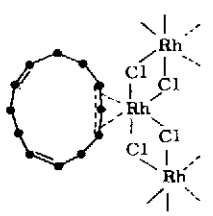
(a) $C_{12}H_{18} + RhCl_3 \rightarrow HCl + C_{12}H_{17}RhCl_2$ *(1)*

The red-brownish precipitate of *(1)* is filtered off from the strongly acidic mother-liquor, washed with ethanol and dried. Complex *(1)*, m.p. 219–222 °C (decomp.), is almost insoluble in the common organic solvents but dissolves in aqueous NH_3. It reacts with *p*-toluidine to give red yellow crystals of *(2)*, m.p. 90–92 °C (decomp.), with simultaneous splitting of the halogen bridge bonds.

(b) $[C_{12}H_{17}RhCl_2]_n + 2n\ C_7H_9N = n[C_{12}H_{17}RhCl_2(C_7H_9N)_2]$ *(2)*

Compound *(1)* is diamagnetic; its infrared spectrum has a peak at 1535 cm^{-1}, which has also been found [2] in several other π-allylic complexes. Furthermore, the infrared spectrum of *(1)* has far more peaks than that of *(2)* because of the greater molecular dissymmetry of *(1)*; in contrast, the π-complex of platinum, $(C_{12}H_{17})_2Pt_2Cl_4$ has an infrared spectrum similar to that of *(2)*.

On the basis of the diamagnetism and the infrared spectrum of *(1)* and of the stoichiometry of reaction (a), we infer that *(1)* is a π-allylic complex. On the account of its insolubility and reaction (b), we believe that *(1)* has a polymeric structure



(1)

with hexacoordinated Rh(III) atoms of the type similar to that proposed for $[(diene)RuX_2]_n$ [3].

Received, July 30th, 1963 [Z 560/383 IE]
German version: Angew. Chem. 75, 861 (1963)

[1] *G. Wilke* et al., Angew. Chem. *75*, 10 (1963); Angew. Chem. internat. Edit. *2*, 105 (1963).

[2] *W. R. McClellan, H. H. Hoehn, H. N. Cripps, E. L. Muetterties*, and *B. W. Howk*, J. Amer. chem. Soc. *83*, 1601 (1961).

[3] *E. W. Abel, M. A. Bennett*, and *G. Wilkinson*, J. chem. Soc. (London) *1959*, 3178.

A New Synthesis of Cyclic Phosphonium Salts

By Dr. G. Märkl

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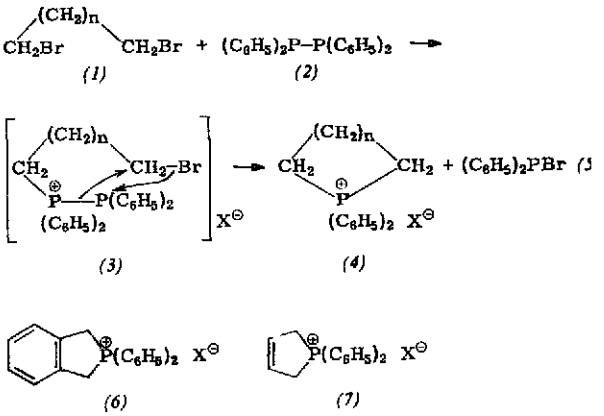
Cleavage of tetraphenylmonoalkyldiphosphonium salts [1,2] to give diphenylalkylphosphines or the phosphonium salts formed therefrom is more suitable for the synthesis of cyclic phosphonium salts than earlier methods [4,5], since tetraphenyldiphosphine *(2)* [3] is readily accessible and is easy to handle. Because of a favorable neighboring group effect, cleavage of *(3)* gives rise almost exclusively to *(4)*.



(4): n=2 [4], X=ClO_4^-, m.p. 114–115 °C, 72 % yield;
n=3 [4], X=Br^-, m.p. 261–262 °C, 66 % yield;
n=4 [4], X=Br^- m.p. 245–247 °C, 54 % yield.

1,2-Bis(dibromomethyl)benzene gives the phosphindoline derivative *(6)* [6], X = ClO_4, m.p. 180–181 °C, in 42 % yield (plus a small high-melting fraction, m.p. > 340 °C); *cis*-1,4-dibromo-2-butene leads to *(7)*, X = ClO_4^-, m.p. 120–121 °C, in 18 % yield.

A solution of 2 moles of *(1)* and 1 mole of *(2)* in *o*-dichlorobenzene is added dropwise to boiling *o*-dichlorobenzene; at the end of the addition, the mixture is boiled for further 10–20 min. After cooling, *(4)* is filtered off. The present yields of over 50 %, based on *(2)*, suggest subsequent reaction of the diphenylbromophosphine *(5)* formed with *(1)* to give *(4)*, by analogy to the reactions of *(5)* with alkyl iodides studied by *H. Hoffmann* [2].

Received, July 29th, 1963 [Z 551/381 IE]
German version: Angew. Chem. 75, 859 (1963)

[1] *K. Issleib* and *A. Tzschach*, Chem. Ber. *92*, 1397 (1959).

[2] *H. Hoffmann, R. Grunewald*, and *L. Horner*, Chem. Ber. *93*, 861 (1960).

[3] See [2] and also *W. Kuchen* and *H. Buchwald*, Chem. Ber. *91*, 2871 (1958).

[4] *G. Märkl*, Angew. Chem. *75*, 669 (1963); Angew. Chem. internat. Edit. *2*, 479 (1963).

[5] *S. O. Grim* and *R. Schaaff*, Angew. Chem. *75*, 669 (1963); Angew. Chem. internat. Edit. *2*, 486 (1963).

[6] *F. G. Mann, J. T. Millar*, and *F. H. C. Stewart*, J. chem. Soc. (London) *1954*, 2832.

Bis-phenoxy-Radicals of the Polyphenyl Series

By Prof. Dr. K. Dimroth, Dr. W. Umbach, and Dr. K. H. Blöcher

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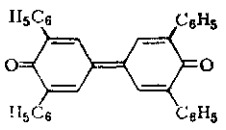
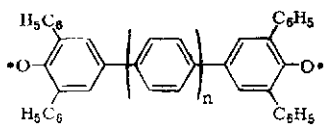
Whereas tetraphenyl-diphenoquinone *(1)* [1] exists predominantly as the quinone – the reddish-green crystals give rise only to an extremely weak EPR-signal – the tetraphenylterphenyl derivative *(2)* and the terphenylquaterphenyl derivative *(3)* [2], which we have obtained as dark-colored crys-

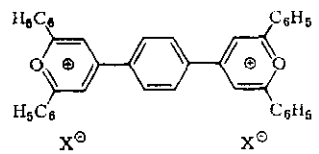


(1)



(2); n = 1
(3); n = 2

talline stable compounds, produce a very strong EPR-signal. Compound *(2)* was obtained from the dipyrylium salt *(4)* by two-fold nitromethane-condensation [3], reduction, diazotization, hydrolysis and dehydrogenation of the bis-phenol. Compound *(3)* was prepared from 2,4,6-triphenylphenol with $SOCl_2$ and $AlCl_3$, followed by dehydrogenation of the bis-phenol, and independently from 2,6-diphenyl-4-(4-bromophenyl)anisole and copper powder, followed by cleavage of the ether, and dehydrogenation.



$X^{\ominus} = ClO_4^{\ominus}, BF_4^{\ominus}$ (4)

The oxidation power of *(3)* is greater than that of *(2)* and of *(1)*, because *(3)* is capable of dehydrogenating the phenol of *(2)* or of *(1)* immediately. The new radicals may be compared with the C-radicals of the type of Tschitschibabin's hydrocarbon. The phenyl substitutens (*ortho* to the oxygen atom) enhance the stability. Bis-phenols of type *(2)* and *(3)* which lack these substituents do not yield stable radicals.

Received, August 2nd, 1963 [Z 558/382 IE]
German version: Angew. Chem. *75*, 860 (1963)

[1] *J. Plesek*, Chem. Listy *50*, 246 (1956); *H. D. Schminke*, Ph. D. Thesis, Universität Marburg, 1961.

[2] *K. H. Blöcher*, Ph. D. Thesis, Universität Marburg, 1961.

[3] *K. Dimroth*, Angew. Chem. *72*, 331 (1960).

Azulenes from Pyrylium Salts and Wittig Reagent

By Prof. Dr. K. Dimroth, Dr. K. H. Wolf, and H. Wache

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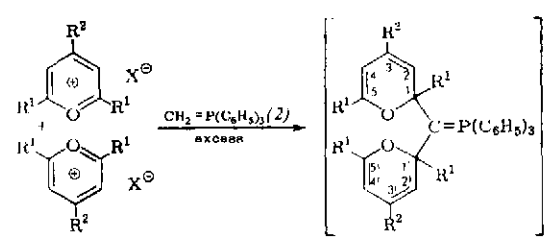
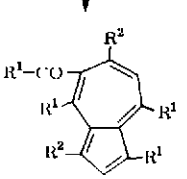
Pyrylium salts *(1)* normally yield benzene derivatives with triphenyl methylene phosphorane *(2)* [1]: in this way, 2,4,6-triphenylpyrylium fluoroborate (or perchlorate) and *(2)* condense in the presence of t-butoxide in t-butanol or in a little acetonitrile to form 1,3,5-triphenylbenzene, 2,3,4,6-tetraphenylpyrylium salts give tetraphenylbenzene (m.p. 217–218 °C), and pentaphenylpyrylium salts give pentaphenylbenzene (m.p. 246–248 °C).



(1) (3)

(1a): $R^1 = R^2 = C_6H_5$
(1b): $R^1 = C_6H_5$; R^2 = p-Cl–C_6H_4
(1c): $R^2 = C_6H_5$; R^1 = p-Br–C_6H_4
$X^{\ominus} = BF_4^{\ominus}$ or $ClO_4^{\ominus}$



(4)

If the 2,4,6-triphenylpyrylium salt *(1a)* is allowed to react with *(2)* in CH_2Cl_2 or in a large quantity of acetonitrile, in which it is relatively soluble, then two molecules of *(1a)* and one of *(2)* condense to form a deep blue azulene *(4)*, m.p. 289 to 290 °C, in about 30 % yield. Its structure follows *inter alia* from its spectrum in the visible region, its fluorescence, infrared and NMR spectra and from the fact that *(4)* gives a colorless salt with acids which reverts to the blue substance on addition of sufficient water or with bases. With *(1b)* and *(1c)*, chloro- or bromo-substituted azulenes are formed. The reaction did not occur with tetraphenyl- and pentaphenylpyrylium salts.

The novel reaction must go through a primary addition product, such as *(3)*, which then undergoes deprotonation, ring-opening, aldol condensation between C-4 and C-5′, and a peculiar transannular C–C bonding between C-4′ and the methylene-carbon of *(2)* with elimination of triphenylphosphine (which we were able to isolate as its adduct with $HgCl_2$, m.p. 285 °C) to form the azulene.

Received, August 2nd, 1963 [Z 557/388 IE
German version: Angew. Chem. *75*, 860 (1963)

[1] *K. Dimroth* and *K. H. Wolf*, unpublished experiments; *G. Märkl*, Angew. Chem. *74*, 696 (1962); Angew. Chem. internat. Edit. *1*, 511 (1962).

The Diazanorcaradiene Ring System [1]

By Dr. Günther Maier

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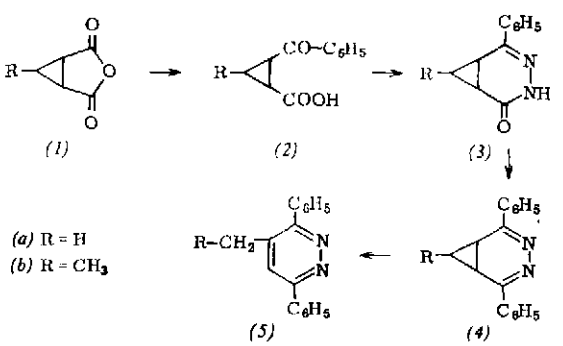
der Technischen Hochschule Karlsruhe (Germany)

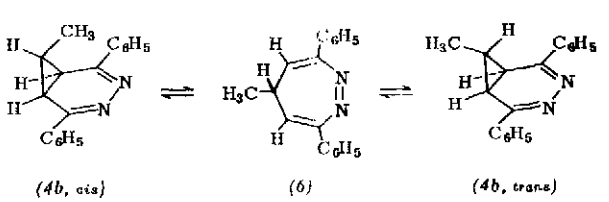
Starting out from cyclopropane-1,2-dicarboxylic anhydride *(1a)* and from the corresponding *cis*- and *trans*-3-methyl anhydrides [*(1b, cis)*, m.p. 91 °C, and *(1b, trans)*] treatment with benzene in the presence of $AlCl_3$ gave the 1-benzoylcyclopropane-2-carboxylic acids *(2)* with the benzoyl group *cis* to the carboxyl group [*(2a)*, m.p. 146 °C; *(2b, cis)*, m.p. 195 °C; *(2b, trans)*, m.p. 135 °C]. Condensation of *(2)* with hydrazine gave the pyridazinone derivatives *(3)* [*(3a)*, m.p. 165 °C; *(3b, cis)*, m.p. 191 °C; *(3b, trans)*, m.p. 174 °C].



(a) R = H
(b) R = CH_3

(1) (2) (3) (5) (4)

Reaction of *(3a)* with phenyl-lithium yielded *(4a)*, m.p. 196 °C (decomp.); *(4a)* is a derivative of diazanorcaradiene as follows from its infrared spectrum (no NH band, C=N double bond band at 1545 cm^{-1}) and NMR spectrum (10 aromatic and 4 aliphatic protons; the latter gave an AB_2X spectrum: $\tau_A = 7.91$; $\tau_B = 7.38$; $\tau_X = 9.77$; $J_{AB} = 9.0$ cps; $J_{AX} = 3.5$ cps; $J_{BX} = 4.8$ cps), and also from the fact that *(4a)* isomerizes with acids to *(5a)*, m.p. 135 °C.



(4b, cis) (6) *(4b, trans)*

Reaction of *(3b, cis)* and *(3b, trans)* with phenyl-lithium gave only one compound, viz. *(4b)*, m.p. 190 °C (decomp.). This finding indicates very rapid equilibration of *(4b, cis)*, *(4b, trans)*, and *(6)*, in complete favor of one of the two norcaradiene derivatives. The NMR spectrum suggests that the isolated compound *(4b)* must have the structure *(4b, cis)*.

The methyl derivative *(4b)* resembles the derivative *(4a)* in its infrared spectrum (no NH band, band at 1540 cm^{-1}), NMR spectrum (10 aromatic protons; methyl group as doublet at 9.4 τ; 3 protons as AB_2-spectrum at 7.2–7.8 τ), and ease of conversion into *(5b)*, m.p. 80 °C. The ultraviolet spectra of *(4a)* and *(4b)* differ very characteristically from the spectra of saturated cyclic azines.

Received, August 2nd, 1963 [Z 573/396 IE]
German version: Angew. Chem. 75, 920 (1963)

[1] A Contribution to the Norcaradiene Problem, Part 2. – Part 1: *G. Maier*, Chem. Ber. *95*, 611 (1962).

1-Mono- and 1,4-Dihalogeno-1,3-butadienes with Predominant cis-Structures [*]

By Dr. H. G. Viehe

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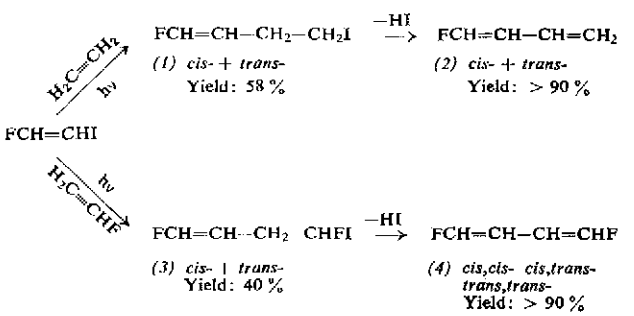
Brussels (Belgium)

Photochemical addition of 2-fluoro-1-iodoethylene [1,2] onto ethylene or fluoroethylene yields the adducts *(1)* and *(3)*, which are converted by loss of hydrogen iodide into 1-fluoro-1,3-butadiene *(2)* and 1,4-difluoro-1,3-butadiene *(4)*, respectively.



The isomers obtained were separated by gas chromatography: *(1)* and *(3)* on Apiezon L/firebrick at 120 °C in a current of nitrogen using a Beckman Megachrom; the *cis*- was desorbed before the *trans*-isomer; *(2)* and *(4)* were separated on β,β'-oxydipropionitrile [3] and di-n-butyl maleate (1:1.85)/firebrick in a current of helium using a Beckman GC 2 instrument, *(2)* at 0 °C and *(4)* at 40 °C; with *(2)*, the *cis*- was desorbed before the *trans*-form; with *(4)*, the relative retention times were *cis,cis*- = 1, *cis,trans*- = 1.16, *trans,trans*- = 1.45. All the isomers were identified by their infrared and ultraviolet spectra, and some of them additionally by their NMR spectra [4].

1,4-Dichloro-1,3-butadiene *(5)*, which is analogous to *(4)* and which was already known as the isomer mixture [5] and as the *trans,trans*-isomer [6], was separated by gas chromatography on Embacel [from May & Baker, 45–60 mesh with 20 % β,β'-oxydipropionitrile [3] + dinonyl phthalate (1:1)] at 100 °C in a current of helium using an F and M 500 instrument.

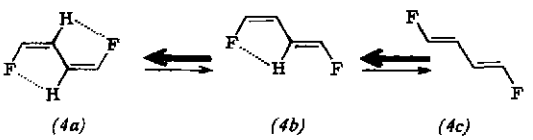
The mixture of *cis*- and *trans*-1-chloro-1,3-butadiene *(6)* [7], which is an analogue of *(2)*, was separated by gas chromatography under the conditions used for *(4)*, but at 20 °C.

Thermal isomerization of the butadienes under investigation in benzene with 1 % iodine at 100 °C showed that the *cis*-isomers are invariably more stable than the *trans*-isomers. Table 1 shows the ratio of isomers at equilibrium and their relative stabilities. Allowance is made in these figures for the fact that the *cis,trans*-isomers occur twice statistically at equilibrium, but only once in the energy ratios.

Table 1. Ratio of isomers after equilibration at 100 °C in benzene + 1 % iodine, and stability ratios RS of the isomers.

(2)	*cis*- = 62 %; *trans*- = 38 %;	RS approx. 1.6:1
(6)	*cis*- = 70 ± 5 %; *trans*- = 30 ± 5 %;	RS approx. 2.3:1
(4)	*cis, cis*- = 43 %; *cis, trans*- = 43 %; *trans, trans*- = 14 %;	RS = 3.4:1.7:1
(5)	*cis, cis*- = 51 %; *cis, trans*- = 40 %; *trans, trans*- = 9 %;	RS = 5.5:2.2:1

The measurements [4] indicated that this predominance of the *cis*-form is due to interaction between the halogen and hydrogen [*(4a)–(4c)*].



(4a) *(4b)* *(4c)*

This leads us to a preliminary working hypothesis which is contrary to the conventional teaching: the forces of attraction (probably van der Waals forces) between substituents predominate in the absence of H···H interaction, such as in pure hydrocarbons, or of extremely high steric requirements, such as in 1,2-diiodoethylene.

Received, August 5th, 1963 [Z 553/386 IE]
German version: Angew. Chem. 75, 793 (1963)

[*] Communication No. IV on Pairs of Geometrical Isomers with Predominant *cis*-Structures. Communication No. III: [1].

[1] *H. G. Viehe, J. Dale,* and *E. Franchimont*, Chem. Ber., in the press.

[2] *H. G. Viehe*, Chem. Ber. *93*, 1697 (1960).

[3] Di-(β-cyanoethyl) ether.

[4] A more extensive report will appear in Chem. Ber.

[5] *W. Reppe, O. Schlichting, K. Klager,* and *T. Toepel*, Liebigs Ann. Chem. *650*, 2080 (1948).

[6] *R. Criegee, W. Horauf,* and *W. D. Schellenberg*, Chem. Ber. *86*, 126 (1953); *E. H. Braye*, personal communication on work to be published in Bull. Soc. chim. Belge.

[7] *A. C. Onitschenko* and *N. J. Aronowa*, Dokl. Akad. Nauk SSSR *132*, 138 (1960).

The Diphenylmethylcarbonium Ion

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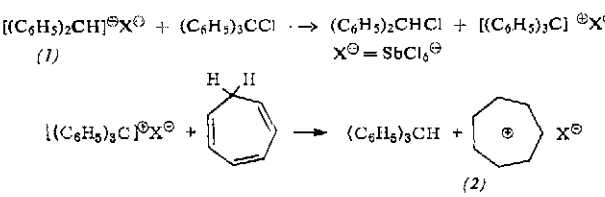
Whereas several solid salts of the triphenylmethylcarbonium ion are known, until now no solid salt of the diphenylmethylcarbonium ion has been prepared [1].

On treatment of diphenylchloromethane with antimony pentachloride in carbon tetrachloride under nitrogen with the exclusion of moisture, the yellow diphenylmethyl hexachloroantimonate *(1)* was obtained.

Compound *(1)* is very hygroscopic, but if moisture is excluded it is stable at room temperature for a short time.

With tropylidene, *(1)* forms diphenylmethane and tropylium hexachloroantimonate *(2)*. Triphenylchloromethane transfers a chloride ion to compound *(1)* to give diphenylchloromethane and triphenylmethyl hexachloroantimonate. This latter compound can subsequently be reacted with tropylidene to yield triphenylmethane and compound *(2)* [2].



Treatmcnt of the diphenylmethylcarbonium ion with diphenyldiazomethane affords tetraphenylethylene as primary product.

Received, August 5th, 1963 [Z 556/385 IE]
German version: Angew. Chem. 75, 921 (1963)

[1] *K. Hafner* and *H. Pelster*, Angew. Chem. *73*, 342 (1961), obtained an orange oil from benzhydrol and HBF_4 in ether.

[2] *H. J. Dauben, Jr., L. R. Honnen*, and *K. U. Harmon*, J. org. Chemistry *25*, 1442 (1960).

A New Degradation of Glucose to Arabinose

By Dr. Manfred Schulz and cand. chem. H. Steinmaus

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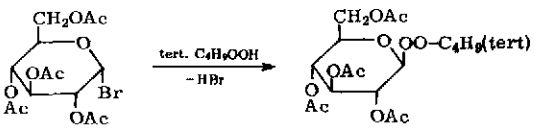
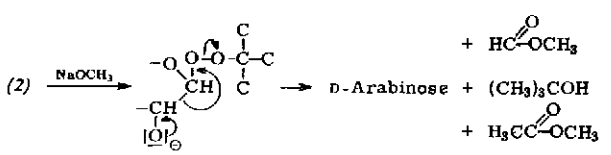
t-Butyl 2,3,4,6-tetra-*O*-acetyl-β-peroxyglucoside *(2)*, m.p. 120 °C, $[\alpha]_D^{25} = -46.8°$ in ethanol, is obtained in 70 % yield by treating α-acetobromoglucose *(1)* with t-butyl hydroperoxide in benzene in the presence of excess silver carbonate at room temperature for 7 hours.



(1) *(2)*

D-Arabinose is obtained in almost quantitative yield by treatment of *(2)* with 0.01 N sodium methoxide at room temperature for 3 days. It was identified by elementary analysis, paper chromatography, osazone formation, and specific rotation.



Carbon atom 1 of the glucose is removed as formic acid, which was identified as methyl formate by gas chromatography and by reduction to formaldehyde and precipitation of same with tetrahydrophthalazine [1]. D-Arabinose is also formed from *(2)* by heating it with a 1:1 mixture of 2N H_2SO_4/ethanol. Experiments have shown that the new sugar degradation is capable of extension for general application.

Received, August 8th, 1963 [Z 569/395 IE]
German version: Angew. Chem. 75, 918 (1963)

[1] *E. Schmitz* and *R. Ohme*, Mber. dtsch. Akad. Wiss. Berlin *1*, 366 (1959).

Formation of Toluene from Benzene and Methane

By Prof. Dr. A. Rieche and Dr. H. Seeboth

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We have examined whether, and to what extent, the hydrogenolysis of toluene *(1)*

$$C_6H_5{-}CH_3 + H_2 \rightleftarrows C_6H_6 + CH_4$$

(1)

over a $NiO\text{-}Al_2O_3$ catalyst in the vapour phase under normal pressure is reversible. At 250–300 °C, some *(1)* resulted from benzene and methane (molecular ratio 1:1 to 1:2). At 350 °C, the yield increased when H_2 was added to the reaction mixture, and decreased with increasing methane concentration. At a molecular ratio $C_6H_6:CH_4:H_2 = 1:2:2$ and a volumetric rate of $\text{benzene}_{\text{liquid}} = 0.15$/hr., we obtained 8 g *(1)* from 100 g benzene. 71.2 g Benzene were unreacted. The remainder of the benzene was converted into methane; therefore *(1)* can also be formed solely from benzene and H_2 (7 % yield).

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Synthesis of Compounds with Covalent Metal-Boron Bonds

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Compounds with stable boron-metal σ-bonds were hitherto unknown. The nature of the bonds in aminoboranes can be compared with those in vinyl compounds [$R_2N{=}B(X){-}$ ⟷ $R_2C{=}C(X){-}$] considering the differences in polarity of these bonds; hence, since vinyl-metal compounds are well known, the possibility of stabilizing a covalent metal-boron bond occurred.

The reaction

$$[(CH_3)_2N]_2BCl + NaMn(CO)_5 \rightarrow [(CH_3)_2N]_2B{-}Mn(CO)_5 + NaCl$$

(1) *(2)* *(3)*

in ether results in the formation of orange-yellow, crystalline bis(dimethylamino)borylmanganese pentacarbonyl *(3)*, decomp. 60 °C. Yellow-orange $C_6H_5[(CH_3)_2N]B{-}Mn(CO)_5$, m.p. 146–150 °C, can be prepared similarly. In benzene solution it is monomeric.

Although $(C_4H_9)_2B{-}Mn(CO)_5$ and $(C_6H_5)_2B{-}Mn(CO)_5$ could not be obtained, the decarbonylated product $[(C_6H_5)_2BMn]_2$ (colorless needles, m.p. 216–218 °C [1]) is isolable.

$(CH_3)_2N{-}B[Mn(CO)_5]_2$ (light orange, soluble in benzene and ether, decomposes above 85 °C) was prepared from *(1)* and two moles of *(2)* and has two metal-boron bonds. On replacing a CO group by $P(C_6H_5)_3$, covalent manganese-boron bonds become stable – even in the absence of $(CH_3)_2N$-groups. The reaction

$$X_2BCl + NaMn(CO)_4P(C_6H_5)_3 \rightarrow X_2B{-}Mn(CO)_4P(C_6H_5)_3 + NaCl$$

led to

$[(CH_3)_2N]_2B{-}Mn(CO)_4P(C_6H_5)_3$, golden yellow, m.p. 125 °C,

$(C_4H_9)_2B{-}Mn(CO)_4P(C_6H_5)_3$, yellow, m.p. 100 °C (decomp.),

$(C_6H_5)_2B{-}Mn(CO)_4P(C_6H_5)_3$, yellow, m.p. 120 °C.

These compounds dissolve in benzene as the monomers, and the B–N- and B–Mn-bonds are the reactive sites of the molecules.

Reactions of boron halides with $Na_2[Fe(CO)_4]$ or $Na[Fe(CO)_3NO]$ proceed more indefinitely. With $Na_2[Fe(CO)_4]$, the tendency to form $[Fe(CO)_4]_3$ predominates. However, $Na[Fe(C_5H_5)(CO)_2]$ reacts with boron halides to give B–Fe-compounds. $R_2B{-}Fe(C_5H_5)(CO)_2$ with R = $(CH_3)_2N$, C_6H_5, and Cl have been isolated.

Received, August 13th, 1963 [Z 568/398 IE]
German version: Angew. Chem. 75, 861 (1963)

[1] $[(C_6H_5)_2BMn]_2$ behaves differently chemically from all other boron-manganese compounds. This is probably due to π-complex formation.

Asymmetric 1,3-Induction during the α-Addition of Immonium Ions and Carboxylate Anions onto Isonitriles

By Doz. Dr. I. Ugi and Dipl.-Chem. K. Offermann

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With the aim of attaining asymmetrically induced peptide syntheses, the steric course of α-aminoalkylation of isonitriles in combination with carboxylic acids [1,2] was studied. Condensation of L-(−)-α-phenethylamine *(1)* with isobutyraldehyde *(2)*, benzoic acid *(3)*, and t-butyl isocyanide *(7)* served as a model. The intermediates *(4)*–*(6)* are formed reversibly from *(1)*–*(3)* and combine with *(7)* to give the α-adducts *(8t)* and *(8e)* [3]. The L-valine derivative *(9t)* is formed from *(8t)* by *O.N*-acyl migration; the D-valine derivative *(9e)* is formed analogously from *(8e)*. The ratio of the amounts of the diastereoisomeric end-products *(9t)* and *(9e)* depends on the concentration, the temperature, and the solvent (Table 1).

In moderately polar solvents [4] (a), the diastereoisomers *(6t)* and *(6e)*, which are stabilized by hydrogen bridges, are formed from *(1)*–*(3)* [5] via the intermediates *(4)* or *(5)*. More *(6t)* is formed than *(6e)*, *i.e.* Q is greater than 1, as the O–C bond is formed more readily on the sterically less hindered side of the C=N double bond (kinetic 1,3-induction [6]).

In solvents of low solvating power, the equilibrium *(6t)* ⇌ *(6e)*, which lies on the side of *(6e)* because of its lower conformational strain, is only slowly established; Q thus approximates to the ratio of the rates of formation of *(6t)* and *(6e)* (a), assuming *(6t)* ⟶ *(8t)* and *(6e)* ⟶ *(8e)*.

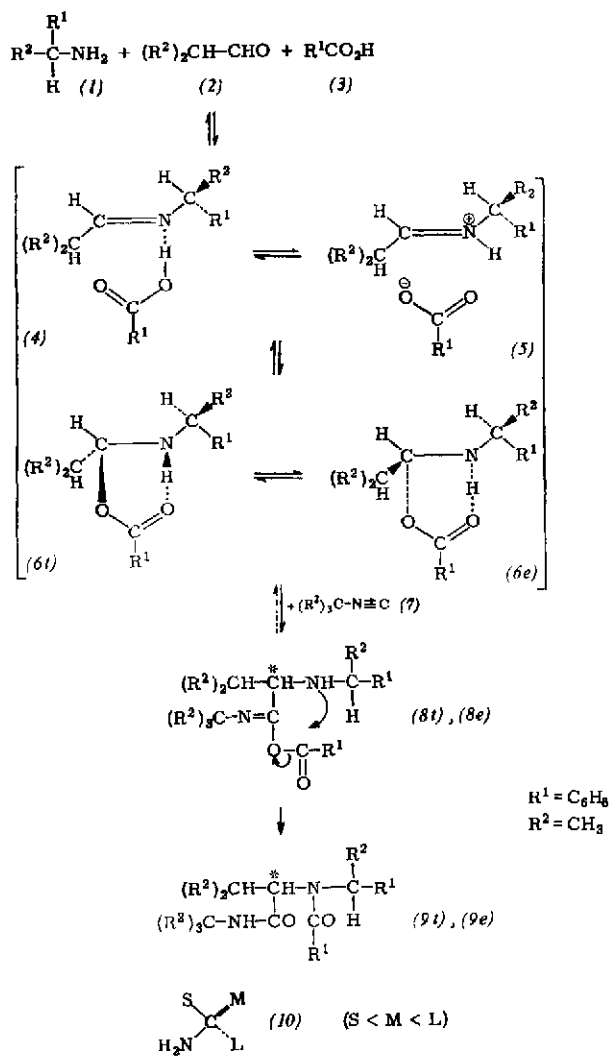

Table 1. Ratio Q = *(9t)*:*(9e)* under various reaction conditions.

	Solvent	Temp. [°C]	Concentration of *(1)*–*(4)* [mole/kg]	Q	Formation of *(8)* predominantly from
(a)	Chloroform	0	0.63	1.41	*(6t)*, *(4)*
(b)	Ethane-1,2-diol	0	0.88	1.82	*(5)*
(c)	Methanol	−40	0.97	0.48	*(6e)*
(d)	Methanol	0	0.15	2.57	*(5)*
(e)	Methanol	0	0.97	1.01	*(5)*, *(6e)*
(f)	Methanol	0	1.80	0.67	*(6e)*
(g)	Methanol	+60	0.97	1.63	*(5)*
(h)	Ethanol	0	0.97	0.47	*(6e)*
(i)	Tetramethylurea	0	0.88	0.44	*(6e)*

In highly polar solvents, such as ethane-1,2-diol (b) in methanol at low concentrations (d) or elevated temperatures (g), Q is determined by the steric course of the α-addition of *(7)* onto *(5)* [2] and, with rapid attainment of the equilibrium *(6t)* ⇌ *(6e)* via *(4)* or *(5)*, also by the *Curtin-Hammett* principle [7]. The situation is similar to that in chloroform. In solvents in which the equilibrium *(6t)* ⇌ *(6e)* is established at a moderate rate, and dissociation to *(5)* is relatively unimportant [(c), (f), (h), (i)], the position of this equilibrium determines the steric course of the complete reaction (thermodynamic 1,3-induction; Q < 1). The influence of the solvent on the hydrogen bridge can affect Q in this case. The possibility that differences in the rate of the *O.N*-acyl migration affect Q cannot be excluded, although it is unlikely that *(8t)* and *(8e)* interchange sufficiently rapidly, either by dissociation to *(7)* and *(4)*–*(6)* or via L-α-phenethylaminoisopropylketene-t-butylimine and *(3)* [2].

Thus, condensation of a primary amine of configuration *(10)* with an aldehyde, a carboxylic acid, and an isonitrile is subject to kinetically controlled asymmetric 1,3-induction and gives predominantly a derivative of an L-α-amino acid, whereas thermodynamically controlled asymmetric 1,3-induction gives preferential formation of the D-α-amino acid derivative.

Received, August 13th, 1963 [Z 566/394 IE]
German version: Angew. Chem. *75*, 917 (1963)

[1] *I. Ugi* and *C. Steinbrückner*, Chem. Ber. *94*, 2802 (1961).

[2] *I. Ugi*, Angew. Chem. *74*, 9 (1962); Angew. Chem. internat. Edit. *1*, 8 (1962).

[3] The diastereoisomers of *(6)*, *(8)*, and *(9)* which would have the *threo*-configuration if the two asymmetric centres were directly linked together are designated as *threo*-forms *(t)*. The *erythro*-forms *(e)* are designated analogously.

[4] Details of further relationships between reaction conditions and asymmetric induction will be reported soon by *I. Ugi* and *K. Offermann* in Liebigs Ann. Chem.; *H. Herlinger*, *H. Walz*, and *I. Ugi* will publish the results of physico-chemical studies of the adducts from carboxylic acids and Schiff's bases in the near future.

[5] Cf. *H. Hellmann* and *G. Opitz*: α-Aminoalkylierung. Verlag Chemie, Weinheim/Bergstr. 1960.

[6] Cf. rules of *Cram* and *Prelog* [7] concerning kinetically-controlled 1,2- and 1,4-induced asymmetric syntheses.

[7] Cf. *E. L. Eliel*: Stereochemistry of Carbon Compounds. McGraw-Hill, New York 1962.

A New Synthesis of Pyrrolidones [1]

By Dr. H. Metzger and Dr. K. Seelert

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An attempt to prepare cyclopropanecarboxylic acid amides from dimethyloxosulfonium methylide *(1)* and acrylic acid anilides [2] surprisingly yielded *N*-arylpyrrolidones.

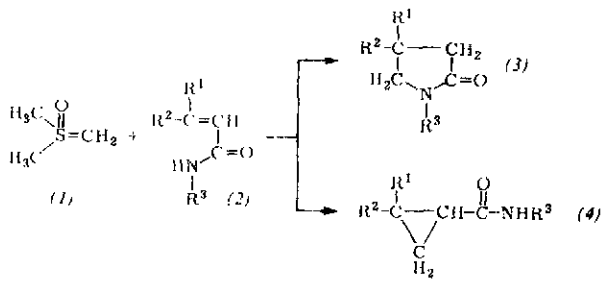
Investigation of this new reaction of compound *(1)* with amides of α,β-unsaturated acids *(2)* showed that the products are pyrrolidones *(3)* or cyclopropanecarboxylic acid

Table 1. Examples of the reaction *(1)* + $R^1R^2C{=}CH{-}CO{-}NHR^3$ *(2)* → *(3)* + *(4)*

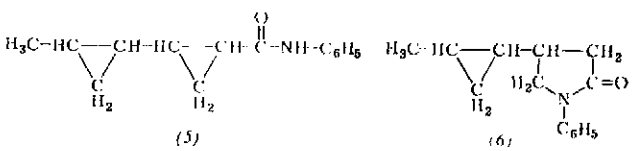
R^1	R^2	R^3	*(3)* Yield [%]	*(3)* B.p. [°C/mm Hg] or m.p. [°C]	*(4)* Yield [%]	*(4)* B.p. [°C/mm Hg] or m.p. [°C]
H	H	H	*ca.* 50	130/12	0	
H	H	CH_3	*ca.* 50	85/10	0	
H	H	C_6H_5	70	69	0	
H	H	$C_6H_4CH_3$ (*p*)	88	88	0	
H	H	$C_6H_3CH_3$(*p*)Cl(*m*)	95	80	0	
CH_3	H	H	61	116/12	0	
CH_3	H	C_6H_5	80	45	11	109
CH_3	CH_3	C_6H_5	45	112/0.4	30	119/0.4
C_6H_5	H	H	0	—	40	188
C_6H_5	H	C_6H_5	70	180/0.2	20	146
$H_3C{-}CH{=}CH$	H	C_6H_5	76[a]	48 [a]	13[b]	155/0.3 [b]

[a] Compound *(6)*. [b] Compound *(5)*.

amides *(4)*, or a mixture of both, depending on the nature of the substituents in the amide *(2)*. Examples are given in Table 1.



The best yields of pyrrolidone derivatives are obtained from acrylic acid arylamides. Cinnamic acid anilide gives a mixture of *(3)* and *(4)* in the ratio 3.5:1. Cinnamic amide on the other hand, yielded only the cyclopropane derivative. With two moles of *(1)* sorbic acid anilide gave compound *(6)* in good yield, together with a small quantity of *(5)*.



The substances were reacted in dimethylsulfoxide or dimethylformamide at temperatures of up to 60 °C. In cyclohexane or benzene we obtained from *(1)* and acrylic acid *p*-toluidide a by-product, m.p. 218 °C, to which we assign the structure *(7)* on the basis of its analysis, infrared and NMR spectra and the formation of butyric acid *p*-toluidide upon Raney-nickel desulfurization.

$OS(CH_2{-}CH_2{-}CONHC_6H_4CH_3)_2$ *(7)*

Amides of saturated acids, *e.g.* benzamide, do not react with compound *(1)* under comparable conditions.

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German version: Angew. Chem. *75*, 919 (1963)

[1] 3rd Communication on *S*-ylids; 2nd Communication: Z. Naturforsch. *18b*, 335 (1963).

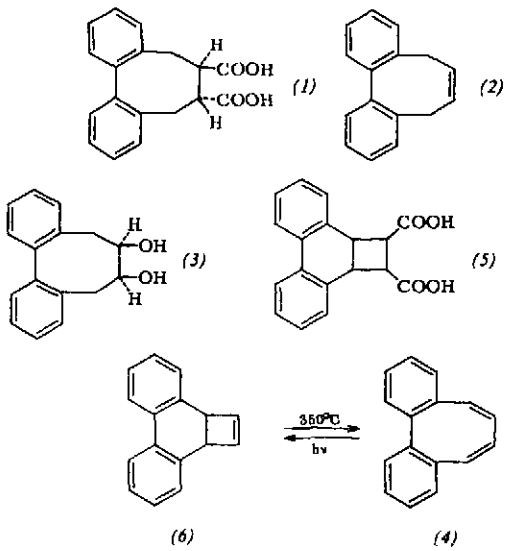
[2] Cf. *E. J. Corey* and *M. Chaykovsky*, J. Amer. chem. Soc. *84*, 867 (1962); Tetrahedron Letters *1963*, 169.

1,2,3,4-Dibenzo-cyclooctatetraene

By Prof. Dr. Emanuel Vogel, Dr. W. Frass, and Dipl.-Chem. J. Wolpers

Institut für Organische Chemie der Universität Köln (Germany)

1,2,3,4-Dibenzo-cyclooctatetraene *(4)* was for the first time prepared from *trans*-1,2,3,4-dibenzo-cycloocta-1,3-diene-6,7-dicarboxylic acid *(1)* [1], which was converted to 1,2,3,4-dibenzo-cycloocta-1,3,6-triene *(2)* by oxidative bis-decarboxylation with lead tetraacetate in the presence of pyridine [2]. Hydroxylation of *(2)* with performic acid gave a mixture of glycols, consisting mainly of *cis*-1,2,3,4-dibenzo-cycloocta-1,3-diene-6,7-diol *(3)* (m.p. 169–170 °C) [3]. The *cis*-configuration of this glycol was shown by its identity with the compound obtained from *(2)* and OsO_4. This unusual *cis*-hydroxylation with performic acid is probably due to a



neighbouring group effect of one of the aromatic rings [4]. The glycol *(3)* was then converted with acetic anhydride to its diacetate (m.p. 110–111 °C) which was pyrolysed at 550 °C *in vacuo*. This gave a 60% yield of *(4)* (m.p. 123 to 124 °C).

Apart from this route, *(4)* could also be made from its valence isomer *(6)*. This compound (m.p. 171–172 °C) is produced in moderate yield when the acid *(5)* derived from the photo-adduct of maleic acid anhydride and phenanthrene [5] is treated with lead tetraacetate under the same conditions as *(1)*. The structure of *(6)* is shown by the NMR spectrum and by oxidative degradation to phenanthrene-9,10-dicarboxylic acid. The thermal isomerisation of *(6)* to *(4)* requires the temperature of 350 °C, which is high compared to the temperature necessary for the splitting of simple cyclobutenes to butadienes. Phenanthrene and acetylene are formed in a side-reaction [6]. The cause of the notable thermal stability of *(6)* is apparently to be found in the fact that the rearrangement of *(6)* to *(4)* does not conform to the stereochemical rule holding for the cyclobutene-butadiene isomerisation by which *cis*-3,4-substituted cyclobutenes selectively yield 1,4-disubstituted butadienes with the *cis-trans*-configuration [7]. If *(4)* is irradiated with ultraviolet light, *(6)* is reformed practically quantitatively [8].

Received, August 19th, 1963 [Z 564/389 IE]
German version: Angew. Chem. *75*, 979 (1963)

[1] *L. V. Dvorken*, *R. B. Smyth*, and *K. Mislow*, J. Amer. chem. Soc. *80*, 486 (1958).

[2] *C. A. Grob*, *M. Ohta*, and *A. Weiss*, Angew. Chem. *70*, 343 (1958).

[3] A glycol isolated together with *(3)* appears to be *trans*-1,2,3,4-dibenzo-cycloocta-1,3-diene-6,7-diol.

[4] *R. Huisgen*, Angew. Chem. *69*, 341 (1957), postulates such a neighbouring group effect to explain the solvolytic reactivity of the tosylate of 1,2-benzo-cyclooctene-4-ol.

[5] *D. Bryce-Smith* and *B. Vickery*, Chem. and Ind. 429 (1961).

[6] Cf. the breakdown of the cyclobutene ring into an olefine- and an acetylene-component, *G. Wittig* and *U. Mayer*, Chem. Ber. *96*, 342 (1963).

[7] *E. Vogel*, Liebigs Ann. Chem. *615*, 14 (1958); *R. Criegee* and *K. Noll*, ibid. *627*, 1 (1959).

[8] For the photochemical work Professor *G. O. Schenck*, Mülheim/Ruhr kindly put apparatus at our disposal, which we gratefully acknowledge here.

Reductive Cleavage of π-Allylpalladium Chloride Complexes [1]

By Dipl.-Chem. H. Christ and Prof. Dr. R. Hüttel

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The yellow di-π-allylpalladium chloride co-ordination compounds $(C_nH_{2n-1}\cdot PdCl)_2$ [2] are readily decomposed by methanolic potassium hydroxide. The compounds are dissolved in methanol, and 1N methanolic alkali is added. The reaction, which starts at room temperature, is complete after warming for 5 minutes and yields palladium metal and an olefin, which can be separated easily by dilution with water. The methoxide ion acts as a reducing agent. The reaction is useful for investigation of the structures of π-allyl complexes of palladium. Examples are given in Table 1.

In experiments 1 and 3, the resulting mixture of olefins was separated by gas chromatography into two isomers, thus demonstrating that the double bond can be formed at both of the terminal allyl carbon atoms – with preference for the more stable 2-isomer. This is also evidence for the structures given for the π-allyl complexes. A control experiment precluded the possibility that the isomeric olefins are altered after their formation under the reaction conditions.

Table 1. Original olefins, π-allyl complexes, and olefins evolved.

No.	Original olefin	π-Allyl complex: Structure of organic constituent	m.p. [°C]	Yield of olefins evolved
1a 1b	2-Methyl-1-pentene *(1)* 2-Methyl-2-pentene *(2)*	1-ethyl-2-methyl-π-allyl	104	19 % *(1)* and 55 % *(2)*
2	3-Ethyl-2-pentene *(3)*	1,3-dimethyl-2-ethyl-π-allyl	130	75 % *(3)*
3a 3b	2,3-Dimethyl-1-butene *(4)* 2,3-Dimethyl-2-butene *(5)*	1,1,2-trimethyl-π-allyl	125	23 % *(4)* and 55 % *(5)*
4	2,4-Dimethyl-2-pentene *(6)*	1-isopropyl-2-methyl-π-allyl	162	82 % 2,4-dimethyl-1-pentene and/or *(6)* [a]
5	2,4,4-Trimethyl-2-pentene *(7)*	1-t-butyl-2-methyl-π-allyl	132	88 % 2,4,4-trimethyl-1-pentene and/or *(7)* [a]
6	1-Methylcycloheptene *(8)*	1,2-pentamethylene-π-allyl	180	76 % *(8)*

a] Not separated.

Received, August 27th, 1963 [Z 574/399 IE]
German version: Angew. Chem. *75*, 921 (1963)

[1] Part V of a series on Olefin-palladium chloride complexes; Part IV: *R. Hüttel* and *H. Christ*, Chem. Ber. *96* (1963), in the press.

[2] *R. Hüttel, J. Kratzer*, and *M. Bechter*, Chem. Ber. *94*, 766 (1961).

A New Preparation of Manganese Tetrafluoride

By Dipl.-Chem. H. Roesky and Prof. Dr. O. Glemser

Anorganisch-Chemisches Institut
der Universität Göttingen (Germany)

Hoppe, Dähne, and *Klemm* [1] recently reported the first preparation of manganese tetrafluoride from manganese(II) and manganese(III) compounds as well as from $LiMnF_5$ and Li_2MnF_6 with elemental fluorine. For example, they obtained about 20 mg of MnF_4 per hour from MnF_2 in a stream of fluorine at 550 °C.

We have since found it possible to obtain larger quantities of MnF_4 relatively quickly by the direct fluorination of manganese powder in a fluidized bed. The fluidized bed is produced in a tube made of pure nickel (10 mm in diameter) at whose lower end a fine-meshed nickel screen is attached to hold back the metal powder. After the apparatus has been swept out with fluorine, about 0.5–1.0 g of manganese powder (particle size 0.062–0.075 mm) is introduced. The apparatus is evacuated before adjusting the flow of fluorine to form a fluidized bed about 10 cm long in the tube [2]. At the same time the nickel tube above this bed is heated to about 600 °C. In less than one minute the manganese powder is converted completely into blue MnF_4, which is deposited in a trap cooled with liquid air.

We were able to confirm that the properties of MnF_4 are those described by the above authors [3]. We wish to thank cand. chem. *K. H. Hellberg* for his assistance.

Received, August 26th, 1963 [Z 571/397 IE]
German version: Angew. Chem. *75*, 920 (1963)

[1] *R. Hoppe, W. Dähne*, and *W. Klemm*, Naturwissenschaften *48*, 429 (1961); Liebigs Ann. Chem. *658*, 1 (1962).

[2] Predetermined in preliminary experiments.

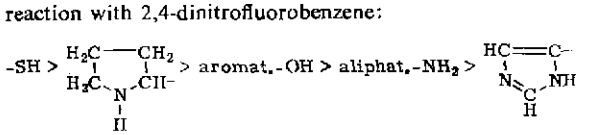
[3] We have not observed the formation of a violet-red smoke ($HMnO_4$) on reaction with water.

CONFERENCE REPORTS

Mechanisms of Enzyme Reactions

On April 26th and 27th, 1963, the 14th Mosbach Colloquium of the Gesellschaft für Physiologische Chemie (German Society for Physiological Chemistry) was held on the above theme [1]. The three main subjects discussed were: protein structure and catalysis, coenzymes, and hydrogen transfer.

K. Wallenfels and *C. Streffer* (Freiburg/Breisgau, Germany) reviewed "the chemical reactivity of proteins". Apart from a few exceptions, all enzyme catalyses are probably variations of or related to acid-base catalysis. It is especially difficult to associate pK values with definite functional groups in a protein, if these have pK values lying close together or if they are spatially close, as in the case of the amino and thiol groups of cysteine, so that there is the chance of interaction between them. Investigation of the nucleophilic reactivity of the functional groups of amino acids yielded the following series for reaction with 2,4-dinitrofluorobenzene:



The specific reactions of SH groups in proteins were dealt with in detail. Thus, inhibition of enzymatic activity by an agent which is usually regarded as specific, such as *p*-chloromercuri-

[1] The proceedings, including discussions, will be published by Springer-Verlag, Heidelberg (Germany).

benzoate, is not to be attributed entirely to reaction with SH groups, since reaction can also take place with disulfide or amino groups. In many cases, so-called specific reagents act on the chain conformation of the protein and eliminate partially or completely the characteristics necessary for enzyme catalysis. In the reaction between 2,4-dinitrofluorobenzene and cysteine or homocysteine, reaction with the SH group is followed by transfer of the dinitrophenyl residue from the SH to the NH_2 group. However, there is no rearrangement if the SH group is separated by more than three methyl groups from the NH_2 group. The dissociation enthalpies also indicate interaction between the SH and NH_2 groups in cysteine. After dissociation of the first proton, the second is evidently associated equally with both groups (SH and NH_2). Dissociation of the combined function of the sulfhydryl and amino groups in cysteine and homocysteine follows special laws.

M. L. Bender (Evanston, Illinois/U.S.A.) spoke on chymotrypsin, one of the serine proteinases. The normal hydrolysis catalysed by this enzyme very probably goes via an acyl-enzyme complex, an ester, which can be detected spectrophotometrically. On the other hand, hydroxylaminolysis or the hydrolysis of hydroxamic acids cannot be explained by this means alone, since model investigations show that hydroxylamine is a stronger nucleophilic agent than the OH group of serine or the imidazole group. The location of these groups at the active site of chymotrypsin (and of other serine proteinases) and their direct participation in the catalysis are postulated. This was deduced from the dependence of the reaction on the pH, the isotope effect, and the influence of photo-oxidation. Groups with pK values of 7 (imidazole, basic form) and 8.5 (possibly a serine hydroxyl group, acidic form) participate in the acylation of the enzyme, whereas only imidazole in the basic form acts in the deacylation of the acyl-enzyme complex. It is assumed that the group with the pK of 8.5 provides the correct orientation of the substrate and of the hydroxyl group which enters into the ester linkage, while the imidazole group functions as an acid-base catalyst.

H. Fasold, U. Gröschl-Stewart, G. Gundlach, and *F. Turba* (Würzburg, Germany) dealt with the relationships between structure and action in hydrolases. In contrast to ribonuclease, the two histidine residues in chymotrypsin do not react with iodoacetic acid or iodoacetamide. The inhibitory action of halogenoacylamino esters of typical substrates or substrate-analogous inhibitors on chymotrypsin was investigated in order to bring the halogenoacyl residue into contact with the active centre as specifically as possible. Amino acid analysis showed that the histidine residues were unaltered but that methionine had reacted with the halogen compound. Hence it follows that methionine is located in the vicinity of the active centre. As an example from the cysteine enzymes (sulfhydryl-carboxyl type as opposed to imidazole-hydroxyl-carboxyl type as seen in serine-histidine enzymes such as chymotrypsin), the dependence on time of ATPase inhibition by [^{14}C]-*N*-ethylmaleimide was studied. The EDTA-sensitive part of the enzyme action (binding centre) is lost first, while the Ca-activated action (catalytic centre) decreases considerably more slowly. In the fingerprint diagram, a cysteine peptide can be associated with the binding centre. In model experiments on the action of cysteine and serine-histidine enzymes, measurement, for example, of the rate of hydrolysis of nitrophenyl acetate effected by histidyl compounds indicates participation of an amide group next to the imidazole ring, which is possibly influenced by a free carboxyl group as in carbobenzoxyglycyl-*m*-aminobenzoyl-glycyl-histidinamide.

B. R. Rabin and *A. P. Mathias* (London, England) related how they were able to show that an acid pair participates in the inhibition of ribonuclease by iodoacetic acid. One of the two acids must be in its basic form (pK 4.85), the other in its acid form (pK 5.55). Reaction of the enzyme with substrate is also coupled via an acid pair. The group functioning as an acid has a pK of 5.22 in the free enzyme and 6.30 in the enzyme-substrate complex; the pK values for the group acting as a base are 6.78 and 8.10. From the above, the influence of organic solvents on the reaction, and alcoholysis, it is concluded that an imidazole pair (probably from histidine residues 12 and 119) is located at the active centre as an acid-base catalyst. The imidazole group in the basic form serves as an acceptor for the proton donated by the attacking nucleophilic agent (water, alcohol), while the second imidazole group acts as hydrogen donor for the 2′-oxygen atom of the substrate and thereby raises the electron affinity of the phosphorus. The reverse reaction is analogous.

H. Witzel (Marburg/Lahn, Germany) supposes on the other hand that direct activation of the 2′-oxygen by the enzyme is out of the question and proposes that the enzyme merely effects protonation of the phosphate anion. An intermediate state with a strongly nucleophilic pentavalent phosphorus atom is supposed to be stabilized by the enzyme in the process. According to this mechanism, the two imidazole groups partaking in the reaction would then protonate the phosphate group and thus raise its electron affinity. The pyrimidine base is then thought to participate in the degradation catalysis (preferential splitting of the 5′-bond before the 3′-bond or of the 2′-bond before the 3′-bond). Stuart models show that direct proton transfer from the 2′-OH group to the 5′-oxygen is possible with the help of the pyrimidine base, but for steric reasons not of a purine base. This could explain the absolute specificity of ribonuclease for the diester of pyrimidine. In the reaction catalysed by chymotrypsin, the enzyme with the serine-OH/imidazole system is supposed to catalyse the nucleophilic reaction, which takes place intramolecularly with ribonuclease with the help of the pyrimidine base. The electrophilic reaction of activating the substrate and the stabilization of the intermediate state then occur in the chymotrypsin reaction within the molecule, but in the ribonuclease reaction are effected by the enzyme itself.

C. Veeger (Amsterdam, Holland) reported on three flavine enzymes. Lipoamide dehydrogenase is modified by incubation with Cu^{2+}. The number of mercapto groups is reduced by two, and the linkage of flavine to the enzyme is weakened. The modified enzyme can no longer catalyse the redox reaction with lipoamide; however, the reduction, for example, of dichlorophenolindophenol proceeds considerably faster than before the modification. Similarly, the formation of the intermediate (flavosemiquinone) necessary for the physiological reaction is no longer possible, but the opposite is true for the other intermediate (completely reduced form of flavine) required for reaction with the dye. NADH-dehydrogenase, which has little cytochrome c reductase activity, is converted into an active cytochrome c reductase above 30 °C. It is not yet known if the reductase activity is an artefact or an active constituent of a complex NADH-dehydrogenase system, from which it is released above 30 °C or by proteolysis. Succinic dehydrogenase reacts with competitive inhibitors to form complexes which can be detected spectroscopically. There were no indications of free radicals in these complexes, which are probably charge-transfer complexes between the oxidized enzyme and the inhibitor. The formation of a flavosemiquinone after addition of succinate to the enzyme was deduced from ESR measurements. However, contrary to information in the literature, it must now be assumed that no free radicals exist in the oxidized enzyme as ESR signals could not be obtained.

P. Hemmerich (Basel, Switzerland) discussed the coordination chemistry of flavo-coenzymes and the importance of non-haem metal ions in the respiratory chain. Analysis of the structural and coordination chemistry of the three redox stages of isoalloxazine showed that the quinone stage has high-energy iminol tautomers, but that the semiquinone and leuco stages have low-energy tautomers. The quinone and semiquinone stages are coplanar, but the leuco stage is not unless in an excited state. The isoalloxazine system has an affinity for metals only after taking up one and only one electron; thus, the quinone stage reacts only with donor metal ions to form stable complexes analogous to oxinates. The semiquinone, however, reacts with all divalent d-metal

ions according to the position of each in the Irving-Williams series. On metal-induced stabilization of the semiquinone, the whole system comproportionates. The spectra of the two groups of flavine chelates differ only slightly. The chelate spectra resemble the spectrum of the protonated semiquinone and are almost identical with the spectrum of succinic dehydrogenase. The metal specificity of flavoproteins for Fe and Mo is explained by the specificity of flavoquinone for hydrophilic donor metal ions. The adenylic acid residue of FAD is of no importance in the coordination chemistry.

L. Jaenicke (Köln, Germany) discussed group transfer as a chemical reaction as exemplified by one-carbon units. The biological reactions of one-carbon units needed by folic acid cofactors can be divided into four classes: 1. hydroxymethylation and transhydroxymethylation, 2. formylation and transformylation, 3. mutual interconversion of C_1 units, and 4. methyl group formation. The splitting of serine by hydroxymethylation induced by diarylethylenediamine (as a model for tetrahydrofolic acid) in the presence of pyridoxal and Al^{3+} was investigated as a model for serine aldolase-catalysed hydroxymethylation. Here the ethylenediamine condenses with serine to form an intermediate complex which is activated by azomethine formation on pyridoxal; simultaneously or later the α,β-C-C bond of serine is broken. The resulting carbonium ion is cyclized to the imidazolidine. A cyclic phosphate was postulated as an intermediate in the formylase reaction. To support this proposal, *N,N'*-diphenylethylenediamine (cyclo)phosphate was synthetized, and its hydrolysis and formylation were investigated. *N*-Formyl-*N,N'*-diarylethylenediamine is produced on formolysis. Presumably an enzyme-*S*-phosphate complex is initially formed from ATP and the enzyme. Formate and folate become attached to this in such a steric configuration that the formate is polarized to a formyl cation and can then attack the nucleophilic nitrogen of the folate. Evidently it goes first to N-5 and only secondarily to N-10.

G. Kohlhaw and *H. Holzer* (Freiburg/Breisgau, Germany) reported on the enzymatic formation of TPP-activated formaldehyde from glyoxylate. On treatment of glyoxylate with thiamine pyrophosphate in the presence of pyruvate oxidase from pig heart, a formaldehyde-thiamine pyrophosphate complex is formed, probably via activated glyoxylate [2-hydroxycarboxymethylthiamine pyrophosphate], with liberation of CO_2. Presumably the activated formaldehyde has the structure of 2-hydroxymethylthiamine pyrophosphate.

Experiments carried out by *H. Holzer* and *W. Schröter* (Freiburg/Breisgau, Germany) in order to elucidate the mechanism of phosphoketolase action indicate the intermediary occurrence of a TPP-activated glycolaldehyde[2-(1,2-dihydroxyethyl)thiamine pyrophosphate] and 2-acetylthiamine pyrophosphate.

J. Knappe and *F. Lynen* (Heidelberg and München, Germany) were able to isolate [$^{14}CO_2$]-biotin (1'-*N*-methoxy-[^{14}C]-carbonylbiotin) from the [^{14}C]-carboxy compound of β-methylcrotonyl carboxylase, while working on CO_2 transfer by biotin enzymes. The [$^{14}CO_2$]-biotin fragment was obtained after treatment with trypsin, diazomethane, and papaine on digestion with biotinidase; a further fragment, 1'-*N*-methoxy-[^{14}C]-carbonylbiocytin, was obtained after hydrolysis with papaine. These results show that the CO_2 in the carboxy enzyme is bound only to the 1'-N atom and not to the carbonyl-C atom of the ureido group as other workers recently supposed. The biotin is linked to the protein by the ε-amino group of a lysine residue.

V. M. Clark (Cambridge, England) indicated the importance of hydroquinone monophosphate esters in oxidative phosphorylation. These can be oxidized to the quinone with primary formation of metaphosphate (the probable phosphorylating agent). Thus, oxidation of 2,3-dimethyl-4-hydroxy-1-naphthyl phosphate in the presence of the mono-(tetrabutylammonium) salt of AMP yields ADP, and ATP can be synthetized by oxidation of the duroquinone ester of ADP in the presence of tetrabutylammonium dihydrogen phosphate. The formation of hydroquinone phosphate esters of vitamins of the quinone group (E, K, and Q) appears possible, if phosphate first adds onto the methylene group formed by base-catalysed cyclization and transesterification follows.

V. Prelog (Zurich, Switzerland) reported on the product and substrate stereospecificity of enzymatic reduction of carbonyl compounds. Certain microorganisms reduce ketones to alcohols with a high degree of stereospecificity. A stereospecific ketone reductase was obtained from *Curvularia falcata* in a highly purified form. Its substrate and stereospecificity were compared with those of a ketone reductase from pig liver and of alcohol dehydrogenase from horse liver. Whereas horse liver ADH transfers the A-hydrogen from reduced pyridine nucleotide, the other two ketone reductases transfer the B-hydrogen. A rule governing the substrate specificity of the A- und B-enzymes was deduced from experiments with about 30 substrates of known absolute configuration. Using this rule, the arrangement of substituents in substrates for the A- and B-enzymes can be specified. The rule depends on the small distance and consequent strong repulsion between the large carboxamide group of the coenzyme and the substituents of the substrate. The spatial structure of the enzyme protein is responsible for the specificity for substrates in which the transferred hydrogen has an equatorial or axial position on cyclohexane. By comparison of the rate of reaction with methylcyclohexanols and -hexanones and with α- and β-decalols and -decalones, the area of the protein surface, which must be free for the reaction and for the binding of the substrate, can be assessed. The carbon skeleton of the substrate molecule may be conceived as part of a diamond lattice whose position relative to the coenzyme and enzyme is determined by the spatial arrangement of the intermediate stage at hydrogen transfer. Hence predictions may be made regarding the reactivity of hitherto unexamined substrates.

G. Pfleiderer (Frankfurt/Main, Germany) synthetized NAD analogues with a substituted purine ring and free from adenine in order to examine the importance of the ADP part of pyridine nucleotides in the binding and activation of nicotinamide adenine dinucleotide by dehydrogenases. Replacement of the amino group by a hydroxyl or mercapto group has no significant influence on coenzyme function. Replacement of adenine by cytosine reduces the rate of reaction, especially for yeast ADH and malic dehydrogenase. Removal of adenine produces a marked fall in reactivity for all dehydrogenases. It was found from comparative investigations that the coenzyme specificity is least pronounced with liver ADH and glutamic dehydrogenase. Model reactions were studied to obtain information on the activation of the coenzyme by the enzyme. Thus, nucleophilic addition of CN^- onto NAD is increased 10- to 20-fold in the presence of lactic dehydrogenase, and the dissociation of sulfite adducts of NAD and NAD analogues is retarded strongly in the presence of dehydrogenases.

H. Sund (Freiburg/Breisgau, Germany) discussed the structure and mode of action of NAD-dependent dehydrogenases. The dissociation of the ADH-NAD^+ complex from yeast ADH is independent of pH. The binding of the substrate to the enzyme is somewhat dependent on pH, below pH 8.5 but not above that. The pH dependence of the total reaction can be explained on the assumption that there are four differently protonated ternary complexes of various activities. The pK-values of these complexes are 6.78, 7.21, and 8.67 and are ascribed to three group, which do not themselves participate in the binding of the substrate, but, because of their degree of protonation, do influence the rate of reaction. They may be located in the vicinity of the bound substrate and are thus able to influence the active site. It is however also possible that these groups take part in the hydrogen and hydrophobic bonds responsible for the conformation of the protein molecule, which enables the reaction to proceed. The relations between molecular structure and enzyme characteristics are seen particularly well in the glutamic dehydrogenase from bovine liver. Diffusion, sedimentation, and viscosity measurements show that this enzyme protein exists in the associated state as an elongated particle with a molecu-

lar weight of about two million. On dissociation, it splits up into symmetrical particles; the smallest, is still enzymatically active and has a molecular weight of about 250000. Some compounds increase dissociation and inhibit enzymatic activity, others increase association and promote activity. These compounds probably react with the functional groups of the enzyme protein or alter its chain conformation. Thus, both the equilibrium between the individual protein moieties and the enzyme catalysis can be influenced without the assumption of a direct relationship between the particle size and enzyme activity, as was originally thought.

Zinc exercises an important role in reactions catalysed by yeast and liver ADH. Any action of zinc on other dehydrogenases dependent upon pyridine nucleotide is apparently based on another mechanism. In the latter, zinc seems to participate neither in the binding of the coenzyme nor in hydrogen transport. It is still an open question whether there are other pyridine-nucleotide-dependent zinc metal dehydrogenases apart from yeast and horse liver ADH.

[VB 718/97 IE]

German version: Angew. Chem. 75, 795 (1963)

Alkylcarbonium and Alkyloxocarbonium Salts

G. A. Olah, Sarnia, Ontario (Canada)

The structures and chemical reactivity of several primary, secondary, and tertiary alkyloxocarbonium (acylium) salts were investigated by infrared and nuclear magnetic resonance spectroscopy (^1H, ^2H, ^{13}C, and ^{19}F) in complexes of the following type:

$[H_3CCO]^{\oplus}[SbF_6]^{\ominus}$, $D_3CCO]^{\oplus}[SbF_6]^{\ominus}$ and $[H_3C^{13}CO]^{\oplus}\,[SbF_6]^{\ominus}$.

The results are compatible with a structure containing a triple bond, in which however the positive charge is not localized completely on the oxygen atom, *i.e.* an oxocarbonium structure $[H_3C{-}C{\equiv}O]^{\oplus}\,[SbF_6]^{\ominus}$ is actually present.

The chemical shift of the hydrogen atoms in the above salt amounts to about 2 ppm, that of the [^{13}C] carbonyl carbon atom to 45 ppm, compared with acetyl fluoride. In solution (liquid HF and SO_2), the salt is in equilibrium with the covalent donor-acceptor complex

The decarbonylation reaction of a *t*-butyloxocarbonium salt (pivalylium salt) was followed spectroscopically.

$$[(CH_3)_3CCO]^{\oplus}\,[SbF_6]^{\ominus} \rightleftharpoons [(CH_3)_3C]^{\oplus}\,[SbF_6]^{\ominus} + CO$$

The stability of trimethylcarbonium hexafluoroantimonate (in solution in SO_2 or SbF_5 at low temperatures) makes it possible to investigate this compound thoroughly. Alkyl fluorides, *e.g.* propyl, butyl, and amyl fluorides readily ionize in SbF_5 to form remarkably stable, solvated SbF_6-salts.

Several stable alkylcarbonium salts $R^{\oplus}\,[SbF_6]^{\ominus}$, perdeuterated complexes, and also those with ^{13}C-labelling on the positive carbon atom were prepared in solution in SbF_5 plus SO_2 and investigated primarily by spectroscopy (infrared, ultraviolet, NMR). The carbonium ions $(H_3C)_2CH^{\oplus}$, $(H_3C)_3\overset{\oplus}{C}$, and $(H_3C)_2\overset{\oplus}{C}{-}CH_2CH_3$ were thereby obtained and characterised for the first time in the form of stable salts. The chemical shift of $\overset{\oplus}{C}H$ amounts to nearly 10 ppm (or 600 cps at 60 Mc), that of $H_2C{-}\overset{\oplus}{C}{-}$ and $H_3C{-}\overset{\oplus}{C}{-}$ to 2 and 4 ppm, respectively, compared with the uncharged groups. The chemical shift in the ion $(CH_3)_3{-}^{13}\overset{\ominus}{C}$, compared with t-butyl fluoride, is 273 ppm (or 4090 cps), and that of the ^{13}C–H coupling in $H_3C{-}^{13}\overset{\oplus}{C}H{-}CH_3$ is 382 cps. This is indicative of sp^2 hybridization of the positively charged carbon atom in the planar carbonium ions.

[Inorganic Chemistry Colloquium at the Technische Hochschule Aachen (Germany), June 24th, 1963] [VB 711/94 IE]

German version: Angew. Chem. 75, 800 (1963)

Polymorphism of Bismuth Oxides

G. Gattow, Göttingen (Germany)

β-$BiO_{1.50}$, which is metastable at room temperature, can be prepared by extremely rapid quenching of thin films of molten bismuth(III) oxide; however, on treating Bi or Bi_2O_3 with C in a graphite boat with oxygen at 800 °C or more, a product with the composition β-$BiO_{\gtrsim 1.50}$ results. Using chemical and X-ray analysis and by investigation of the thermal decomposition under isobaric conditions, the phase range of the β-modification of bismuth(III) oxide from $BiO_{1.50}$ to $BiO_{1.75}$ was determined. Structural investigations showed that the β-modification crystallizes in the space group $P\bar{4}b2$–D_{2d}^7 and is a two-dimensional superstructure of the high-temperature modification (δ-Bi_2O_3); the crystal structure of the latter was determined at 750 °C. The lattice dimensions with the reliability factors were: for β-$BiO_{1.50}$: $a = 10.95 \pm 0.02$ Å, $c = 5.63 \pm 0.01$ Å; $R_{hkl} = 0{,}04_6$, and for β-$BiO_{1.75}$: $a = 10.96 \pm 0.02$ Å, $c = 5.64 \pm 0.01$ Å; $R_{hkl} = 0.05_2$.

Consideration of the crystal structure of β-$BiO_{1.50}$ shows that the β-modification can absorb oxygen continuously into the lattice without alteration of the symmetry until the composition $BiO_{1.75}$ is attained. This value corresponds to the upper phase boundary of the β-modification.

The transformations of the normal (α-, β-, δ-Bi_2O_3) and oxygen-enriched bismuth(III) oxides were investigated by differential thermal analysis, X-ray photographs, *etc.*, and the transformation sequences drawn up. The heats of transformation were of the order $L_t = 2.0 \pm 0.5$ kcal/mole for δ-$Bi_2O_3 \rightarrow \beta$-$Bi_2O_3$, $L_t = 6.4 \pm 0.8$ kcal/mole for β-$Bi_2O_3 \rightarrow \alpha$-$Bi_2O_3$, and $L_t = 8.4 \pm 0.3$ kcal/mole for α-$Bi_2O_3 \rightleftharpoons \delta$-$Bi_2O_3$ at the appropriate transition temperature.

Starting from β-$BiO_{1.75}$, the γ-modification of bismuth(III) oxide can be prepared free from other oxides. It has the composition $BiO_{1.667}$ and crystallizes in the cubic system with a body-centred lattice and with $a = 10.250 \pm 0.008$ Å. The metastable modifications of β-Bi_2O_3, γ-Bi_2O_3 and δ-Bi_2O_3 can be stabilized by addition of oxides of other metals.

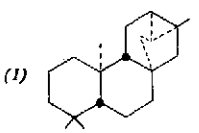
[Inorganic Chemistry Colloquium at the Technische Hochschule Aachen (Germany) June 25th, 1963] [VB 722/99 IE]

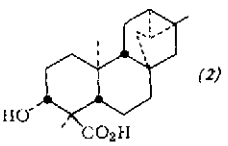
German version: Angew. Chem. 75, 799 (1963)

Recent Investigations on Diterpenes

G. Ourisson, Strasbourg (France) [1]

A number of new diterpenes have been isolated from *Trachylobium verrucosum* (Gaertn.) Oliv. (*Caesalpiniae*), *i.e.* the plant from which Madagascar copal can be obtained. Chemical and spectroscopic investigations showed that a new pentacyclic skeleton is present in some of these diterpenes. Tetracyclic compounds containing the kaurane skeleton, and bicyclic compounds also occur.





The absolute configuration at all the asymmetric centres was determined by correlation with (−)-kaurene. The new pentacyclic skeleton is cyclokaurane *(1)* [2]. Cyclokauranolic acid *(2)* was cited as an example of the new diterpenes.

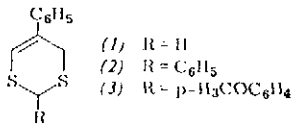
[Karlsruher Chemische Gesellschaft (Germany), June 27th, 1963] [VB 739/101 IE]

German version: Angew. Chem. 75, 940 (1963)

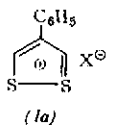
[1] Experimental work by *G. Hugel, L. Lods, J. M. Mellor*, and *D. W. Theobald.*

[2] Note added September 26th, 1963: The name of the pentacyclic skeleton *(1)* has now been changed, at the suggestion of Dr. *K. Overton* (Glasgow), to *trachylobane.*

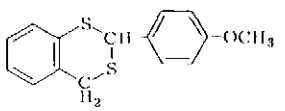
The formation of 1,2-dithiolium salts from 1,3-dithiacyclohexenes by dehydrogenation with ring-contraction is described by *A. Lütteringhaus, M. Mohr*, and *N. Engelhard*. Dehydrogenation of the 1,3-dithiacyclohexenes *(1)* to *(4)*, which are readily prepared from 1,3-dithiacyclohexan-5-one derivatives, using SO_2Cl_2 in ether/acetic acid or more smoothly with Br_2/acetic acid leads to the 1,2-dithiolium salts *(1a)* and *(4a)*. 4-Phenyl-1,2-dithiolium perchlorate [*(1a)*, X = ClO_4], m.p. 202–204 °C (decomp.), bright yellow needles, is formed from *(1)*, *(2)*, or *(3)* in 12–21 % yield; its bromide



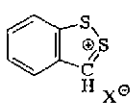
(1) R = H
(2) R = C_6H_5
(3) R = p-$H_3COC_6H_4$



(1a)



(4)



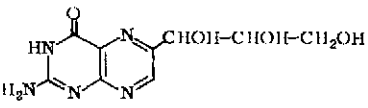
(4a)

(X = Br): m.p. 228–234 °C (decomp.), yellow flakes, yield 46–50 %; its iodide (X = I): m.p. 218–225 °C (decomp.), red crystals. Benzo-1,2-dithiolium bromide [*(4a)*, X = Br], m.p. 174–175 °C, is formed from *(4)*, yellow crystals, yield 55 to 60 %; its perchlorate (X = ClO_4): m.p. 173–175 °C (decomp.), yield 40 %. / Liebigs Ann. Chem. *661*, 84 (1963) / Ma.
[Rd 530/149 IE]

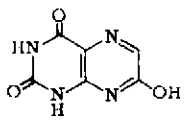
Possible methods for detecting Contergan® and Doriden® were investigated by *W. Paulus* and *R. Keymer* subsequent to a fatal case of poisoning, in which an overdose of both hypnotics was suspected. Both Contergan and Doriden give color reactions on fusion with resorcinol, in the hydroxamic acid test, and with Zwikker's reagent. Contergan gives a crystalline precipitate with iron and copper salt solutions, while Doriden gives no distinct precipitate. Doriden can be detected on paper chromatograms (R_f = 0.86) by spraying with mercuric nitrate solution. Both substances may be determined together by means of thin-layer chromatography on silica gel. On spraying with benzidine/potassium iodide solution, Contergan gives dark blue spots (R_f = 0.25) and Doriden gives golden-yellow spots lined with dark-blue (R_f = 0.67). Despite their similar structure, the infrared spectra of the two substances show characteristic differences, *e.g.* Contergan does not show the band at 2900 cm^{-1} given by Doriden. / Arch. Toxikol. *20*, 38 (1963) / –R.
[Rd 587/160 IE]

The synthesis and degradation of biogenic amines by enzymatic transamination have been examined by *K. Hasse* and *G. Schmid* with soluble enzymes from dialysed extracts of lower (*Neurospora crassa*) and higher plants (pea seedlings, *etc.*). The transamination was followed by estimation of the amines. Substrates of the transaminases are monoamines (tyramine, 3-hydroxytyramine, histamine, L-norephedrine), polyamines (putrescine, cadaverine, spermidine, spermine), and their partially acylated products, as well as carbonyl compounds corresponding to these amines. Deamination and amination products in the reversible transaminase reaction amine ⇌ α-keto acid were characterized; some were isolated as derivates [*e.g.* putrescine/γ-aminobutyraldehyde (–H_2O: Δ^1-pyrroline) as the diamine picrate, m.p. 250 °C (decomp.); the *o*-aminobenzaldehyde condensation product as picrate, m.p. 167 °C (decomp.)]. α-Ketoglutaric acid and pyruvic acid are the principle α-keto acids involved. / Biochem. Z. *337*, 69 (1963) / –De.
[Rd 581/163 IE]

The pteridines in bee pupae have been investigated by *H. Rembold* and *L. Buschmann*. They extracted 2000 *pupae* with 3 % trichloracetic acid and separated the extract by chromatography. It contained *inter alia* the hitherto unknown pteridines neopterine *(1)* and violapterine *(2)*. It is assumed that *(1)* is a precursor and that *(2)* is a metabolite of biopterine. / Liebigs Annn. Chem. *662*, 72 (1963) / –Kr.
[Rd 580/162 IE]



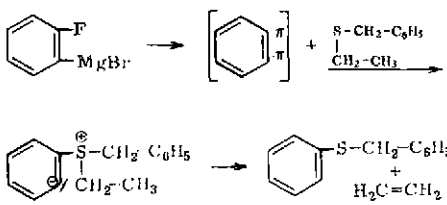
(1)



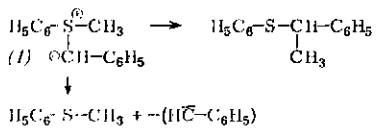
(2)

Chronic insidious mercury poisoning in dental practice has previously been reported only rarely in the literature. Two cases of poisoning from the same practice have recently been described by *S. Preussner, H.-P. Klöcking*, and *G. Bast*. Careless handling of mercury in preparing amalgam fillings was the origin of the illness; the residual mercury was allowed to collect in cracks in the floor producing a concentration of 0.175 mg/m³ in the air of the room. The prime symptoms were psychic changes – increased excitability, restlessness, and insomnia as well as severe headaches; in both cases, the changes in the mucous membrane of the mouth which are typical of chronic mercury poisoning were absent. The urinary excretion of Hg was considerably raised; it was increased further by sulfur bath treatment and in one case also by dithioglycerol injection. After 1½ years, the urinary Hg-levels lay within the normal range; however, restlessness, insomnia, and occasional severe headaches remained as residual symptoms of the poisoning. / Arch. Toxikol. *20*, 12 (1963) / –R.
[Rd 586/166 IE]

The reaction of *o*-fluorophenylmagnesium bromide with thioethers leads, according to *H. Hellmann* and *D. Eberle*, via dehydrobenzene (benzyne) to ylide compounds, which are altered primarily by Hofmann degradation. Details of the



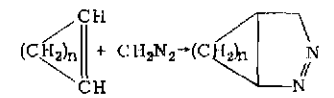
reaction steps are not yet known. When there is no hydrogen in the β-position, the ylide *(1)* is stabilized by a Stevens rearrangement and/or carbene elimination. With *p*-nitro-



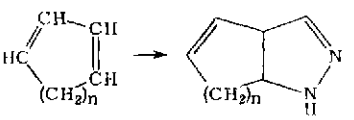
benzyl alkyl sulfides, the charge on the ylide is neutralized preferably by carbene elimination. / Liebigs Ann. Chem. *662*, 188 (1963) / –Kr.
[Rd 579/169 IE]

The relationship between the concentration of free amino acids and the development of tumors in tissues has been investigated by *F. Anders* and co-workers. Raising the free amino acid concentration in susceptible plant or animal tissue can cause a great increase in tumor formation in the tissue. Glutamic and aspartic acids, which are probably involved in nucleotide biosynthesis, are particularly effective. RNA production is stimulated by injection of amino acids into such tissue, the RNA content rising under these circumstances to about ten times the normal level. Protein biosynthesis increases correspondingly. A mechanism for tumor development based on these observations is discussed. / Experientia (Basel) *19*, 219 (1963) / –Re.
[Rd 605/172 IE]

Cyclo-additions of diazomethane onto unsaturated hydrocarbons were studied by *H. Paul, I. Lange*, and *A. Kausmann*. Diazomethane reacts at room temperature in the dark with the simple cycloalkenes *(1)–(3)*, n = 2, 3, or 4, in ether to give the Δ^1-pyrazolines *(4)–(6)*, which are often very stable, but sometimes isomerize readily to the Δ^2-form. The yields diminish with increasing ring-strain (42, 20, 1%). Cyclic dienes always react with only one mole of CH_2N_2; unstable



(1)–(3) *(4)–(6)*



(7), (8) (n = 1, 2)

bicyclic Δ^2-pyrazolines *(7)* and *(8)* can be isolated. Dicyclopentadiene reacts exclusively at the strained double bond to yield a very stable Δ^1-pyrazoline (28%). Methylenecycloalkanes (methylenecyclobutane, -pentane, -hexane, -heptane) give moderate yields of spiropyrazolines. / Z. Chem. *3*, 61 (1963). / –Ma. [Rd 583/167 1E]

Reactions with Na-hydrazide/hydrazine, a powerful reducing agent, were studied by *T. Kauffmann, C. Kosel*, and *W. Sohoeneck*. In contrast to hydrazine, the mixture reduces (in the absence of O_2) several unsaturated polycyclic hydrocarbons; isolated C=C-bonds remain intact. The reductions are carried out at 0–55 °C in benzene or ether (Caution! occasional decomposition): *trans*-stilbene → dibenzyl in 92% yield; 1,4-distyrylbenzene → 4-phenethyl-1-styrylbenzene (at 0 °C), 95.5%, or 1,4-diphenethylbenzene (at 50–55 °C), 93%; 1,4-diphenyl-1,3-butadiene → 1,4-diphenylbutane, 43%; cyclooctatetraene → 1,3,5-cyclooctatriene, 85%; phenanthrene → 9,10-dihydrophenanthrene, 92%; tetracene → 9,10-dihydrotetracene, 84%. / Chem. Ber. *96*, 999 (1963) / –Ma. [Rd 583a/168 1E]

BOOK REVIEWS

Encyclopedia of Plant Physiology, Springer Verlag, Berlin/Heidelberg, 1960. Vol. V: The Assimilation of Carbon Dioxide. Edit. by *A. Pirson*. In two parts, not sold separately. Part 1, with 331 Figs., xl, 1013 pages (545 of these in English), Gr.-8°, 1960. Part 2, 309 Figs., xvi, 868 pages (139 in English) Gr.-8°, 1960. Cloth-bound, DM 530.– (about $135.–) Subscription price DM 424.– (about $106.–).

"Scientific encyclopedias are expensive and already outdated at the time of publication." This is a frequent criticism. It applies, however, only to encyclopedias which have been carelessly compiled, which are badly written, or for which there is no justifiable demand. It should be stated right here, therefore, that Volume 5, "Assimilation of Carbon Dioxide," is excellent. Certainly DM 530 is a considerable price for a single investigator. However, once he has acquired the 1900 pages of the two parts of this volume, he will find that their usefulness is priceless. Professor *Pirson* has persuaded 41 leading specialists, some of them with world-wide reputations, to cooperate, and he himself has seen to it that each contribution conforms to the purpose of such an encyclopedia, so that it is neither a thoughtless collocation of the literature nor an all-too-narrow description of the works of one author. The German editor's work is all the more to be appreciated since some of the most important articles are written in English. English-writing authors had to be included if, as was the desire of publisher and editors, only the best would do. Each of the many chapters has its own list of references with full titles. A 57-page index of authors, as well as German-English and English-German subject indexes are placed at the end of the second part. Because not all scientific expressions start with the same letter in English and in German, this double index is indeed a necessity for easy use by English scholars.

Of all aspects of plant physiology, photosynthesis is one of the most difficult to comprehend, because it involves problems in biochemistry as well as biophysics. Accordingly, the rich contents of this volume are subdivided approximately as follows: carbon dioxide in nature, 83 pages; gas exchange in plants, 150 pages; biochemistry and structure of plastids, 324 pages; physics and chemistry of photosynthesis, 450 pages; general physiology and ecology, 566 pages, photo- and chemosynthesis in bacteria, 166 pages.

Is it worthwhile purchasing a handbook devoted to a field like photosynthesis where fast progress might soon put it out of date? The answer is simple. First, progress has not been fast if we consider the fundamental ideas. Actually, the handbook helps to understand how slowly the main thoughts have developed, and how seemingly surprising discoveries had their foundations laid through decades of work by many investigators. Second, it is not so difficult to keep informed about the newest literature; at least nearly everyone tries to. But without the help of this encyclopedia, it has become virtually impossible to establish whether something still valid has been reported, let us say, between 1910 and 1960 about a partial problem which happens to be in fashion today.

Anyone who intends to take part in any aspect whatever of research on photosynthesis has to acquaint himself with dismayingly scattered literature. One of the more important advantages of this volume is that perhaps there is the good chance that some half-forgotten, or out-of-the-way information, which is to be found here in countless examples, may instigate some new line of investigation. Furthermore, in this book, several authors discuss the same fundamental questions in different contexts. Thus, the student is offered an opportunity to acquire a critical insight into the subject which, without the handbook, he may never attain for sheer lack of time.

In Germany at least, there is nothing which could replace the services of this encyclopedia. Many publications on photosynthesis have appeared in that country which have caused raised eyebrows abroad. About such controversial matters, too, one might profitably consult the handbook. The chemist or physicist who is only interested in the central problem of energy conversion may be inclined to consider the few chapters on ecology, climatic influences, and similar topics as superfluous. But let us assume, for instance, that we shall soon get affirmative knowledge about plant-like forms of life on Mars; where else but in these studies on the influence of environment on the type and behavior of photosynthesizing cells could we find the necessary material for comparison?

The quality of the paper, the print, and the 640 figures are as good as we have come to expect from the Springer publishing house. *H. Gaffron* [NB 12/45 1E]

Modern Methods of Plant Analysis, by *H. F. Linskens* and *M. V. Tracey*, planned by *K. Paech* and *M. V. Tracey*, Vol. V., (compiled from contributions by various specialists). Springer-Verlag, Berlin-Göttingen-Heidelberg, 1962. 1st Edit., XXVIII + 536 pp., linen DM 98. (about $ 25.–).

This volume continues the work commenced by *Paech* and *Tracey*, the merits and failings of which have already been discussed by this reviewer [1]. At that time, an early con-

[1] Vols. 1, 3, and 4: Angew. Chem. *69*, 74 (1957); Vol. 2: ibid. *67*, 736 (1955).

tinuation of the four volumes originally planned was hoped for. This volume represents a supplement to the first volume (published in 1956) and contains chapters on methods developed since that time, such as gas and thin-layer chromatography. However, it goes far beyond the limits indicated by the title, since, for example, methods of tissue and cell culture are dealt with in an admittedly well-written chapter. On the other hand, the intended function of the book is again in question: is it intended to be a laboratory handbook containing full working instructions or to be a treatise on the theory of the methods and a working guide to the literature containing the practical procedures? The contributions alternate between one conception and the other. In view of the variety of authors involved in the task, it is, perhaps not surprising that the heterogeneity criticized earlier is continued in the new volume. Nevertheless, at the same time this is well atoned for by the high quality of most of the chapters.

In view of the fact that monographs of all sizes dealing with particular analytical techniques (*e.g.* chromatography) are now commonplace in every laboratory, it would be space saving, in the reviewer's opinion, if such themes were avoided in general and only dealt with where there is real necessity. It is essential to get away from the idea that it is possible in practice to produce a handbook that is both comprehensive and short. In scientific writing today, the decisive question is no longer whether the publication can be sold. What is important is whether a new publication will prove a help or a burden to the active scientist. *K. Mothes* [NB 71/61 IE]

Grundriss der technischen organischen Chemie (Outline of Organic Chemical Technology) by *A. Rieche*. S. Hirzel Verlag, Leipzig 1961. 2nd Edit. XVIII, 549 pp., 151 illustr., bound DM 24.60 (about $6.25).

In the second edition of this textbook appearing five years after the first [1], the choice and arrangement of the subject matter has remained substantially unaltered. The latest developments in the field of natural gas and petroleum processing are included. New chapters on organic dyestuffs, dyeing and calico printing, tanning and leather manufacture, plant protectives, and explosives have been added. The textbook has thus acquired greater scope, embracing almost the entire field of organic chemical technology.

It is to be commended that the newer developments arising from the switch-over from coal to petroleum and from acetylene to olefins as starting materials in industrial syntheses have been taken largely into consideration; *e.g.* the production of acetaldehyde from ethylene, of butadiene from butane, and of acetylene by pyrolysis of hydrocarbons.

The reviewer believes that, because of the bewildering number of technical processes that are in existence, this book could have given the student more precise differentiation between purely historical processes (the discussions of which should be severely restricted), processes in full-scale production, and processes still in the development stage, and he suggests that the description of outdated processes, such as the hydrogenation of acetylene to ethylene, the production of ethylene from ethanol, or of acetone from acetic acid, could be shortened or entirely omitted. The detailed treatment of the Fischer-Tropsch process and the hydrogenation of coal could also be considerably streamlined.

In addition, condensation would be welcomed in the chapters on organic coloring matters in favor of the dyestuffs used at present as opposed to the historical treatment given (natural coloring materials).

In the Herz synthesis (p. 484), chlorination of the nucleus also occurs. The formation of benanthrone (p. 491) can be explained by the mechanism proposed by *Meerwein*. The constitution of diazo compounds (p. 496) is explained nowadays in disfavor of *Hantzsch*'s conception. Reactive dyestuffs (p. 505) deserve a fuller description in view of their importance. In the section on pigment dyestuffs (p. 509), the importance of saturation vat-dyes and quinacridone should be pointed out. The view of the author, that new pigment dyes have not been developed, is not borne out by the large volume of more recent patent literature. In the sphere of medical preparations, arsenic compounds are now superceded. On the other hand, it would be desirable to have an indication of sulfanilamides as blood sugar depressants.

These critical comments are not intended to detract from the positive impression conveyed by this book. In conclusion, it can be stated that it offers the student a broad picture of organic chemical technology correct in all the important fundamentals and can be recommended to him as a basis for the study of the subject. *A. Sieglitz* [NB 28/54 IE]

[1] 1st Edition: See Angew. Chem. *69*, 75 (1957).

Die quantitative Bestimmung der Alkaloide in Drogen und Drogenzubereitungen (Quantitative Determination of Alkaloids in Drugs and Drug Preparations) by *Otto-Erich Schulz* and *F. Zymalkowski*. Vol. 47 in the series "Chemical Analysis", edited by *G. Jander*. Ferdinand Enke Verlag, Stuttgart, 1960, 1st edit., X, 295 pp., 27 illustr., 29 tables, cloth-bound DM 77.– (about $20.–).

The quantitative determination of alkaloids, particularly in drugs, is an important field of pharmaceutical analysis, in which the producer, dealer, and user are equally interested. The difficulties involved in the actual determination of the alkaloids are generally much less acute than those of their initial isolation and purification. On the one hand, most drugs contain a large number of alkaloids, which are closely related chemically, but of which only some are of interest from the pharmaceutical point of view, and on the other, they may be accompanied by a wide variety of other materials whose presence frequently increases the difficulties of separation. The first section of this monograph is general and covers the principles of methods of isolation and determination. Besides the classical methods of alkaloid extraction, methods employing column chromatography, ion-exchange, countercurrent distribution, and paper chromatography are covered in detail; besides gravimetric and titrimetric methods of determination, colorimetric, photometric, and polarographic methods are dealt with. The second part is specialized and is devoted to consideration of individual drugs. In each case, the properties of the most important alkaloids and materials accompanying them are first discussed in order to make the proposed method of assay understandable. The following descriptions of assay procedures are so detailed that reference to the original work can mostly be dispensed with.

This well-prepared work fills a gap in the scientific literature and should prove of considerable value in all laboratories engaged in pharmaceutical analysis for gaining preliminary insight into proposed methods of determination.

H. Böhme [NB 46/55 IE]

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Kinetics and Mechanism of 1,3-Dipolar Cycloadditions [*]

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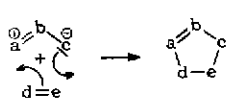
Criteria for the mechanism of 1,3-dipolar cycloadditions which lead to 5-membered rings are provided by the stereoselectivity observed with cis-trans isomeric dipolarophiles, by the effect of solvent and substituents on the rate constants, by the activation parameters, and by orientation phenomena. A concerted addition, which can also be described in terms of molecular orbitals and in which the two new σ-bonds are formed simultaneously, although not necessarily at equal rates, offers the best explanation of the experimental facts.

The concept of "cycloaddition" gives a formal description of an overall reaction but not a mechanistic interpretation. Any discussion of the mechanism of the 1,3-dipolar addition must be viewed against the background of mechanistic interpretation of other cycloadditions which lead to three-, four-, or six-membered rings. Recent studies have shown that cyclopropanes can be formed from an alkene + carbene via at least two mechanisms. Likewise, two reaction paths exist for the coupling of two alkenes to give cyclobutanes, and different stereoselectivities are observed.

A preceding review [1], described various 1,3-cycloadditions which follow the scheme 3 + 2 → 5. Our studies of the mechanism of addition have been carried out exclusively with 1,3-dipoles which have internal octet stabilization according to the definition given elsewhere [1]; hence the following discussion is limited to 1,3-dipolar cycloadditions of this type.

A. Confrontation of Possible Mechanisms

The principal question is whether the two new σ-bonds, which lead to the uncharged five-membered ring on fusion of the 1,3-dipole *a-b-c* with the dipolarophile *d-e*, are closed simultaneously or one after the other.



The experimental criteria discussed below favor a multi-center or concerted reaction with a cyclic electron shift, as symbolized by the arrows in the above diagram. One-step reactions of this type (the Diels-Alder reaction and the Claisen and Cope rearrangements are well-known examples) have been referred to in the United States as "no-mechanism reactions" [2]. This terminology was born of "Scherz, Satire, Ironie und tiefere Bedeutung" [**] and implies the principal impossibility of arriving at a direct mechanistic proof. The energy profile contains a single activation peak between reactants and products; it offers no opportunity for interception. The fact that alternative mechanisms can be excluded from consideration brightens somewhat the pessimism implicit in the name "no-mechanism reaction".

The 1,3-dipole is always an ambivalent compound, which either displays electrophilic and nucleophilic activity in positions 1 and 3 or reacts in the 1,3-position as a spin-coupled biradical. The mesomerism of the octet and sextet resonance structures of the 1,3-dipole (formulated below for diazoalkanes) results in charge compensation or charge exchange, respectively, which makes it impossible to identify unequivocally an electrophilic and nucleophilic center. In other words, the question whether the cyclic electron shift formulated above

Octet structures

$$\underline{N}\equiv\overset{\oplus}{\underline{N}}-\overset{\ominus}{\underline{C}}R_2 \longleftrightarrow |\overset{\ominus}{\underline{N}}=\overset{\oplus}{\underline{N}}=CR_2$$

Sextet structures

$$\overset{\oplus}{\underline{N}}=\underline{N}-\overset{\ominus}{\underline{C}}R_2 \longleftrightarrow |\underline{N}=\underline{N}-\overset{\oplus}{\underline{C}}R_2 \longleftrightarrow |\underline{N}-\underline{N}=CR_2$$

[*] Extended version of a lecture given at the Annual Meeting of the Dechema in Frankfurt/Main on June 14th, 1962, and of the Max Tishler Lecture at Harvard University on December 10th, 1962.

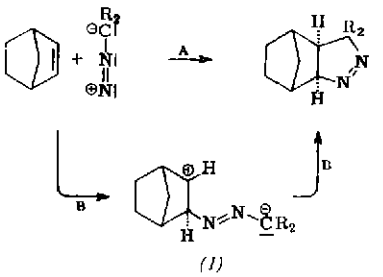
[1] *R. Huisgen*, Angew. Chem. *75*, 604 (1963); Angew. Chem. internat. Edit. *2*, 565 (1963).

[2] Cf. *W. v. E. Doering* and *W. R. Roth*, Tetrahedron *18*, 67 (1962).

[**] Play by *Ch. D. Grabbe* (1827).

takes place clockwise or anticlockwise is meaningless. Neither is it meaningful to regard the "biradical" reaction path as an alternative, as long as the event is completed within the framework of a singlet state.

The example of the addition of a diazoalkane onto angularly strained, and thus energy-rich, double bonds of the bicycloheptene type [3] may be used to compare the one-step, concerted addition A with the two-step addition B in which the two new σ-bonds are formed one after the other. In the latter case the energy profile for the addition shows a dip corresponding to the intermediate *(1)* (Figure 1). Incidentally, ordinary nonconjugated alkenes are sluggish in their reaction with diazoalkanes.



(1)

Since the olefinic double bond is nucleophilic, the diazoalkane should function as an electrophilic reagent in the rate-determining primary process of the two-stage scheme B. Additions of nucleophilic cyanide or sulfite

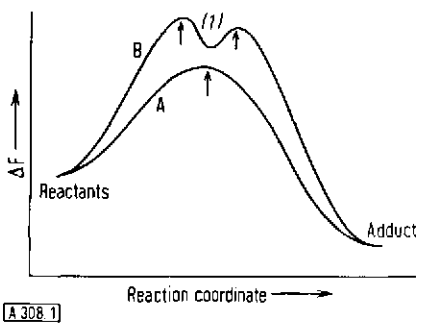
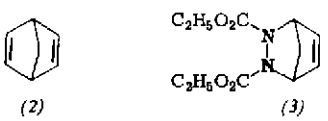


Fig. 1. Energy profiles for the one-step and two-step cycloaddition. The arrows denote transition states.

ion onto the outer nitrogen of diazoalkanes are known [4]; their ease is a function of the degree to which the carbanion charge at the carbon of the diazoalkane is stabilized by substituents. However, the order of reactivity of substituted diazomethanes, as displayed in their additions onto the model compounds *(2)* and *(3)* is opposite to that which would be expected for reaction path B [5]. The introduction of carbonyl substituents, which efficiently distribute the negative charge in the



(2) *(3)*

[3] *K. Alder* and *G. Stein*, Liebigs Ann. Chem. *485*, 211 (1931); *K. Ziegler*, *H. Sauer*, *L. Bruns*, *H. Froitzheim-Kühlhorn*, and *J. Schneider*, ibid. *589*, 122 (1954).

[4] Review: *R. Huisgen*, Angew. Chem. *67*, 453 (1955).

[5] *R. Fleischmann*, unpublished results, Universität München, 1957/58.

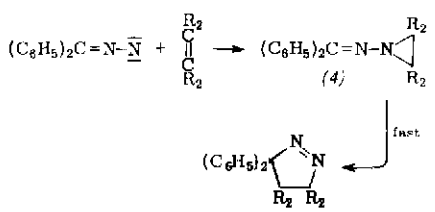
intermediate *(1)*, reduces the addition tendency of the diazoalkane; the presence of two carbonyl groups makes the diazoalkane completely inactive (Table 1).

Table 1. Rates of addition of diazoalkanes onto the angularly strained double bond systems *(2)* and *(3)* [5].

Diazoalkane	Rate of addition
$H_2C{-}N_2$, $(C_6H_5)_2C{-}N_2$	rapid
$C_2H_5O_2C{-}CH{-}N_2$	rather slow
$C_6H_5{-}CO{-}CH{-}N_2$	slow
$pNO_2C_6H_4{-}CO{-}CH{-}N_2$	very slow
$CH_3{-}CO{-}C(C_2H_5O_2C){-}N_2$	no addition

The correlation observed is in agreement with a synchronous closure of both bonds according to path A. Assuming a one-step mechanism, the decreasing reactivity of the diazoalkanes corresponds to increasing stabilization of the ground state. The conclusions drawn from this activity sequence led us during 1957 and 1958 to the general concept of 1,3-dipolar cycloaddition.

Another interpretation, which is difficult to refute in principle, states that the outer nitrogen of the 1,3-dipole first combines with the multiple bond to form a three-membered ring. According to this theory, a rapid intramolecular rearrangement would lead to the five-membered ring. If this were true, then perhaps a longer lifetime would be expected for the primary adducts with diazoalkanes *(4)*, which exhibit the characteristics of hydrazones. Furthermore, contrary to the experimental findings, the rate of addition of triple-bond dipolarophiles should be much lower than with double bonds because of the higher ring strain of the initial adduct. Finally, the 1,3-dipoles without double bond in the sextet structure like azomethine ylides or nitrones cannot display the 1,1-reactivity necessary for the formation of the three-membered ring.



B. Dependence on the Solvent

The result of the primary step of path B is the zwitterion *(1)* whose rather distant formal charges are, contrary to the diazoalkane itself, separated by a tetrahedral carbon atom and, therefore, no longer exchangeable. The formation of such a zwitterion should be greatly facilitated by good solvents for ions. Reactions which are associated with an increase in charge separation are known to exhibit a strong enhancement of rate with rising polarity of the solvent [6]. On the other hand, little or no rate change with solvent polarity would be anticipated for the case of the concerted process A.

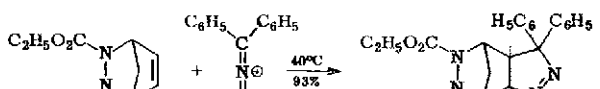
[6] In the reaction of triethylamine with ethyl iodide, the rate constants range over 3.5 orders of magnitude, depending on the polarity of the solvent: *N. Menschutkin*, Z. physik. Chem. 6, 41 (1890); *H. G. Grimm*, *H. Ruf*, and *H. Wolff*, ibid. B *13*, 301 (1931).

Table 2 contains the rate constants for two cycloadditions of diphenyldiazomethane in various solvents [7], one onto the angularly strained double bond of *(3)* (Reaction 1), and the second onto dimethyl fumarate (Reaction 2). A function of the dielectric constant ε serves here as a rough measure of the polarity of the solvent [8]. Both series of rate constants do not exhibit the steep rise expected for the two-step path B; instead, the influence of polarity of the solvent is insignificant.

Table 2. Rate constants for the addition of diphenyldiazomethane onto the cyclopentadiene-azodicarboxylic ester adduct *(3)* (Reaction 1) and onto dimethyl fumarate (Reaction 2) at 40 °C in various solvents [7].

Solvent	$\frac{\varepsilon - 1}{2\varepsilon + 1}$	$k_2 \times 10^4$ (Reaction 1)	$k_2 \times 10^2$ (Reaction 2)
Benzene	0.22	2.43	1.44
Dioxane	0.22	2.93	1.15
Ethyl acetate	0.39	2.27	1.25
Methoxyethanol	0.46	3.64	3.70
Acetone	0.47	2.38	1.10
Acetonitrile	0.48	2.61	2.63
Dimethylformamide	0.48	2.90	2.45

Is this absence of a solvent effect consistent with the concerted addition according to Scheme A (p. 634)? Should not the loss of the formal charges of the diazoalkane during the course of the reaction lead to an inverse solvent dependence? The term "1,3-dipole" should not be understood to imply that these substances have a high electric moment in the ground state. On the contrary, the charge distribution between the two resonance structures with electron octets, already referred to above, reduces the dipole moment of diphenyldiazomethane to 1.42 D, instead of the 6–7 D expected for a single resonance structure. The addition onto the strained double-bond system of *(3)* is not accompanied by an appreciable change in charge separation, as is shown by the electric moments (Scheme 1).



(3) μ = 3.09 μ = 1.42 μ = 3.20 D

Scheme 1. Electric moments in the addition of diphenyldiazomethane onto a strained double bond.

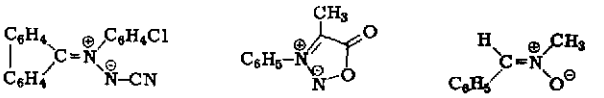
The solvent dependence of the union of a 1,3-dipole and a dipolarophile should be zero, provided the following relationship applies [8,9]:

$$\frac{\mu^2_{\text{1,3-dipole}}}{MV_{\text{1,3-dipole}}} + \frac{\mu^2_{\text{dipolarophile}}}{MV_{\text{dipolarophile}}} = \frac{\mu^2_{\text{transition state}}}{MV_{\text{transition state}}}$$

(for approximation, the molecular weight can be used instead of the molar volume MV)

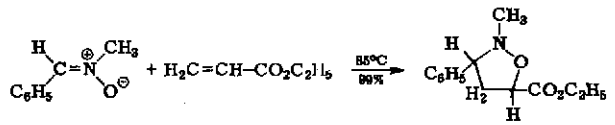
In the case of the diphenyldiazomethane addition cited above, the calculation gives $\mu_{\text{transition state}} = 4.6$ D. If the concerted addition corresponds to a continuous transition of the components into the adduct, then the moment of the transition state (which cannot be measured) should lie between that of the adduct and that of the orientation complex of the components. The moment of the latter would be expected to be 4.4 D [cf. *(31)*]. The transition state thus appears to be only slightly more polar.

The absence or small extent of solvent dependence is typical of 1,3-dipolar additions. The addition of phenyl azide (μ = 1.56 D) onto *(3)* (μ = 3.09 D) to form 98 % adduct (μ = 3.26) shows almost no effect due to the solvent polarity [10]. A weak inverse dependence on the polarity of the solvent is observed, however, if the charge compensation of the 1,3-dipole is less complete than in phenyl azide, as for example in the azomethine imines



(5) μ = 6.7 *(6)* μ = 6.57 *(7)* μ = 3.55 D

(5) and *(6)* or the nitrone *(7)*. In the case of *(5)*, the rate constant for the addition onto dimethyl acetylenedicarboxylate decreases by a factor of 6 when the solvent is changed from benzene to dimethylformamide [11]. With *(6)* and *(7)*, the solvent effects are likewise small; the addition of *(7)* onto ethyl acrylate may again be formulated in terms of dipole moments (Scheme 2).



(7) μ = 3.55 μ = 1.76 μ = 2.48 D

Scheme 2. Electric moments in the addition of *C*-phenyl-*N*-methylnitrone onto ethyl acrylate.

A transition state with μ = 5.4 D (calculated) would lead one to expect no dependence on the solvent. The small moment of the adduct would suggest a smaller moment than 5.4 D for the transition state; if toluene is substituted for ethanol, the rate constant is lowered by a factor of 5.7 as a result of the decrease in charge separation during the activation process [12]. Here, the values of log k for eight solvents show a fairly linear relationship to the empirical polarity function Z [13] of the solvent. In view of the low order of magnitude of the solvent effect, activation parameters have not been measured.

The 1,3-addition of ozone, which has a particularly low dipole moment (0.53 D), onto carbon-carbon multiple bonds is undoubtedly accompanied by an increase in charge separation. The moments of primary ozonides are still unknown. The few kinetic data available in the literature show the expected small positive influence of the solvent. Ozone reacts with benzene at −28 °C in nitromethane three times faster than in chloroform [14], and at +25 °C in acetic acid 3.2 times faster than in carbon tetrachloride [15].

[7] *R. Huisgen, H. Stangl, H. J. Sturm*, and *H. Wagenhofer*. Angew. Chem. *73*, 170 (1961).

[8] *J. G. Kirkwood*, J. chem. Physics 2, 351 (1934).

[9] Cf. *S. Glasstone, K. J. Laidler*, and *H. Eyring*: The Theory of Rate Processes. McGraw-Hill, New York 1941, p. 422.

[10] *H. Stangl* and *H. Wagenhofer*, unpublished results, Universität München, 1960.

[11] *A. Eckell*, Ph.D. Thesis, Universität München, 1962.

[12] *H. Seidl*, unpublished results, Universität München, 1962.

[13] *E. Kosower*, J. Amer. chem. Soc. *80*, 3253 (1958).

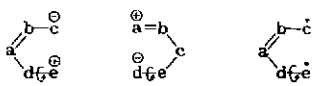
[14] *F. L. J. Sixma, H. Boer*, and *J. P. Wibaut*, Rec. Trav. chim. Pays-Bas *70*, 1005 (1951).

[15] *T. W. Nakagawa, L. J. Andrews*, and *R. M. Keefer*, J. Amer. chem. Soc. *82*, 269 (1960).

Ozonolysis of benzene in nitromethane at −28 °C is accelerated by a factor of 3.5 in the presence of 0.2 M aluminum chloride or ferric chloride [14]. This effect is too small as to lend any support to the assumption that the ozone enters into an initial, electrophilic two-center addition to form an open-chain zwitterion [14]. An increase in solvent polarity due to the addition of the Lewis acid is more probable.

C. Steric Course of the Addition

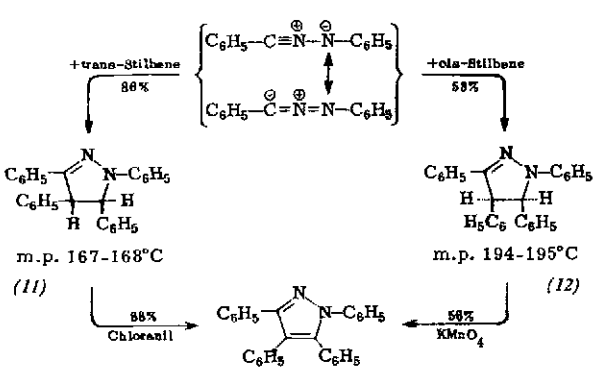
If the two new σ-bonds are closed simultaneously during the cycloaddition, the result must be a stereoselective *cis*-addition. On the other hand, if the coupling with a dipolarophilic double bond *d=e* is accomplished in two steps, then the bond *d-e* should assume single-bond character in the intermediate; this applies equally to intermediates which result from electrophilic *(8)*, nucleophilic *(9)*, or radical *(10)* primary attack. The



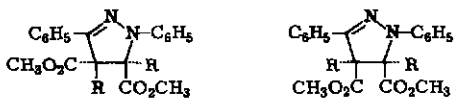
(8) *(9)* *(10)*

energy required to start rotation about this single bond is relatively low. Thus, when an intermediate of type *(8)* to *(10)* is involved, a certain proportion of the molecules should undergo rotation around the *d-e* bond axis prior to ring closure. If one starts with *cis-trans* isomeric alkenes as dipolarophiles *d=e*, then this phenomenon must result in non-stereoselective addition. In the extreme, geometric isomers should both yield either an identical adduct or one and the same mixture of diastereoisomeric adducts.

The addition of diphenyl(nitrile imine) (liberated from benzphenylhydrazidoyl chloride with triethylamine) to *cis*- or *trans*-stilbene yields the pure, *i.e.* mutually uncontaminated, diastereoisomeric Δ²-pyrazolines *(11)* and *(12)*. Both of these compounds can be dehydrogenated to the same tetraphenylpyrazole [16].



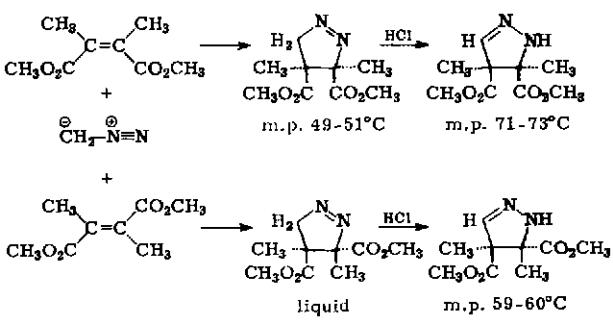
If a lack of stereoselectivity is observed, it must be scrutinized whether subsequent epimerization of the primary adduct has occurred. Thus, decomposition of 2,5-diphenyltetrazole [also a source of diphenyl (nitrile imine)] in dimethyl maleate at 165 °C, yields only 4 % of *(14)*. The mixture contains mostly the *trans*-adduct *(13)*, which is also formed in 88 % yield when the decomposition is carried out in dimethyl fumarate. It has in fact been proven that *(14)* is converted into the thermodynamically more stable compound *(13)* in the presence of basic catalysts. This epimerization, which is initiated by the removal of a proton, is no longer possible with the adduct *(16)* from dimethyl dimethylmaleate. Hence, additions of diphenyl(nitrile imine) onto dimethyl dimethylfumarate and dimethylmaleate proceed stereoselectively to form *(15)* and *(16)*, respectively [16].



(13) R = H *(14)*
(15) R = CH_3 *(16)*

The fact that a *cis*-addition is actually involved here is confirmed by the nuclear magnetic resonance spectra of adducts *(11)* to *(14)*. The coupling of two hydrogen atoms to neighboring carbon atoms is known to depend on the dihedral angle [17]. In a planar five-membered ring, the value of this angle is 0 ° for the tertiary hydrogens present at the 4- and 5-positions of the pyrazoline ring in *(12)* and *(14)*. However, in *(11)* and *(13)*, it is 120 °, so that the degree of coupling is smaller. In fact, the coupling constant J is 11.9 and 13.0 cps, respectively, for the *cis*-compounds *(12)* and *(14)*, and 4.9 cps for each of the *trans*-pyrazolines *(11)* and *(13)*.

All the cycloadditions of octet-stabilized 1,3-dipoles examined so far show similar stereoselectivity. Benzonitrile-*N*-oxide gives diastereoisomeric isoxazolines on addition to fumaric and maleic esters, as well as to mesaconic and citraconic esters [18]. As an example of diazonium betaines, diazomethane may be cited, for it adds stereoselectively onto dimethyl dimethylfumarate and dimethylmaleate [19].



C-Biphenylene-[*N*(α)-*p*-chlorophenyl]-*N*(β)-cyanoazomethine imine *(5)* combines with dimethyl fumarate and dimethyl maleate to give diastereoisomeric, crystalline pyrazolidines in 82 % and 93 % yield, respectively [11]. 3,4-Dihydroisoquinoline-*N*-(*p*-nitrophenyl)imine *(17)* reacts stereoselectively with fumaronitrile and maleonitrile, producing the respective adducts nearly quantitatively with no admixtures of their diastereomers [20].

[16] *R. Huisgen, M. Seidel, G. Wallbillich*, and *H. Knupfer*, Tetrahedron *17*, 3 (1962).

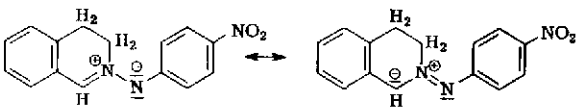
[17] *M. Karplus*, J. chem. Physics *30*, 11 (1959); cf. *H. Conroy*, Advances org. Chem. *2*, 265, 310 (1960).

[18] *A. Quilico, G. Stagno d'Alcontres*, and *P. Grünanger*, Gazz. chim. ital. *80*, 479 (1950); *A. Quilico* and *P. Grünanger*, ibid. *82*, 140 (1952).

[19] *K. v. Auwers* and *E. Cauer*, Liebigs Ann. Chem. *470*, 284 (1929); *K. v. Auwers* and *F. König*, ibid. *496*, 27 (1932).

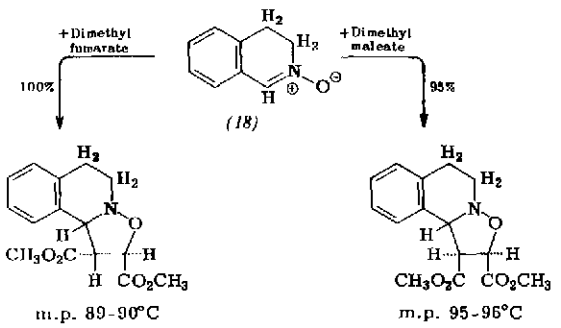
[20] *R. Grashey*, unpublished results, Universität München, 1959/60.

The same is true when *cis*- or *trans*-dibenzoylethylene is used as a dipolarophile.



(17)

In the nitrone series, 3,4-dihydroisoquinoline-*N*-oxide *(18)* gives practically quantitative yields of diastereoisomeric isoxazolidines with dimethyl fumarate or maleate [20].



(18)

In one individual case, the proof of a stereoselective *cis*-addition is always tempered by the possibility that ring closure of the intermediates *(8)* to *(10)* could occur more rapidly than rotation about the *d*-*e* bond axis. However, experience gained with some two dozen examples, in which a stereospecific course was observed without a single exception, weighs heavily against this hypothesis. Thus, stereoselectivity is a valuable criterion for the concerted nature of 1,3-dipolar addition.

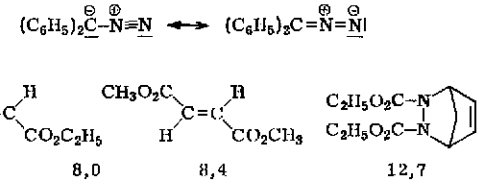
However, it may be an unwarranted simplification to say that the concerted process must necessarily be associated with the one-step addition scheme (A, page 634). One can also conceive of a case in which fixation of the configuration of the dipolarophile *d*=*e* results from the electrostatic attraction of the positive and negative charge centers of *(8)* or *(9)*. This intermediate would be related to an oriented ion pair, and rotation about the *d*-*e* axis would be suppressed. In order to ensure stereoselective addition, the charge centers would have to be electrostatically bound right from the very beginning of the activation process. This would correspond to a concerted addition, however. So far, the experimental data do not require the assumption of a trough in the energy profile of the cycloaddition corresponding to such an ion-pair intermediate. Nevertheless, it should be pointed out that participation of an intermediate in the concerted process is also conceivable.

D. Activation Parameters

Unlike two-center reactions, multi-center or concerted reactions require a high degree of order in the transition state, *i.e.* at the peak of the activation barrier; the reactants must be precisely aligned with respect to each other, otherwise the reaction will not go. This is equivalent to saying that the lock will be closed with a low expenditure of energy only when the key is fitted into it properly. The interplay of entropy and enthalpy controls the rate-determining activation process. For the reasons mentioned, concerted processes generally exhibit large negative entropies of activation ($\Delta S^{\ddagger}$) and only moderate enthalpy requirements.

Let us now proceed to test 1,3-dipolar cycloadditions against this general criterion for a concerted process. Cycloadditions of diphenyldiazomethane onto various activated alkenes do in fact have unusually large negative entropies of activation [7], as determined from kinetic measurements at various temperatures (Table 3). We are not dealing with a unique case, since the finding is quite general. For example, phenyl azide adds onto the angularly strained double bond of norbornene in CCl_4 with $\Delta H^{\ddagger} = 15.2$ kcal and $\Delta S^{\ddagger} = -29$ cal/deg. [21].

Table 3. Eyring parameters for some 1,3-dipolar cycloadditions of diphenyldiazomethane to C=C double bonds in dimethylformamide [7].



$\Delta H^{\ddagger}$[kcal]	8,0	8,4	12,7
$\Delta S^{\ddagger}$[cal/deg.]	-43	-39	-34

Additions of 1,3-dipoles "without a double bond" (cf. [1] for definition) display the same kinetic characteristics (Table 4). The high negative entropy values leave no doubt that effective collisions with the correct orientation occur only rarely. The reactions of ozone fit well into the overall picture of the activation parameters.

Table 4. Eyring parameters for 1,3-dipolar cycloadditions of the azomethine imine [22,23] and nitrone series [12] and of ozone [15].

	$\Delta H^{\ddagger}$ [kcal]	$\Delta S^{\ddagger}$ [cal/degree]
C-Biphenylene-*N*(α)-*p*-chlorophenyl-*N*(β)-cyanoazomethine imine *(5)* (in chlorobenzene)		
+ ethyl acrylate	12.5	−35
styrene	15.6	−31
phenyl isocyanate	12.1	−33
N-Phenyl-*C*-methylsydnone *(6)* (in *p*-cymene)		
+ ethyl phenylpropiolate	18.3	−29
dimethyl acetylenedicarboxylate	14.7	−31
C-Phenyl-*N*-methylnitrone *(7)* (in toluene)		
+ methyl methacrylate	15.7	−32
2-vinylpyridine	18.3	−29
Ozone (in carbon tetrachloride)		
+ benzene	13.2	−23
mesitylene	10.7	−22

E. Activity Series of Dipolarophilic Systems

Comparison of the activities of dipolarophilic systems is of both theoretical and practical importance. If such relative reactivities were known, it could be predicted whether a particular 1,3-dipolar addition would be

[21] *G. Szeimies*, unpublished results, Universität München, 1962.

[22] *M. V. George* and *A. S. Kende*, unpublished results, Universität München, 1962.

[23] *H. Gotthardt*, unpublished results, Universität München, 1962.

possible or not. Moreover, in cases where several dipolarophilic structural elements are found in the same molecule, the reaction site could be predicted.

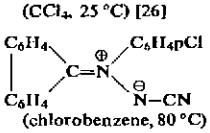
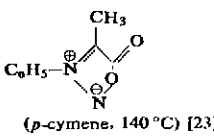
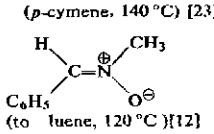
A measure of the ability to undergo addition is the reaction rate constant. Direct kinetic measurement – a great variety of methods have been used to determine concentrations – is possible only if the 1,3-dipole is sufficiently stable and the cycloaddition is accompanied by less than 10 % side reactions. Benzonitrile-*N*-oxide, for example, dimerizes rapidly to diphenylfuroxan, and diphenyl(nitrile imine) cannot even be isolated. Hence we used a competition method: pairs of dipolarophiles were allowed to compete in a known molar ratio for the 1,3-dipole, which was generated *in situ*; analysis of the product, which was usually carried out by quantitative infrared technique, gave the relative rates of addition.

Instead of presenting the entire bulk of material in tabular form, it is more appropriate to discuss selected kinetic data from specific points of view. In this way, similarities in the reactivity of 1,3-dipoles, as well as deviations from common behavior, will be unveiled.

1. Electronic Substituent Effects

The most striking phenomenon observed here is the promoting effect that conjugation exerts on the dipolarophilic activity of all multiple bonds. Table 5 gives a list of the rate constants for additions of various dipoles onto an alkylethylene, styrene, and acrylic ester. To facilitate comparison, all the k_2 values are related to that for acrylic ester, which is taken as 100.

Table 5. Relative rate constants for the cycloadditions of various 1,3-dipoles onto monosubstituted ethylenes (relative to k_2 for acrylic ester = 100).

1,3-dipole (solvent, temperature)	k_2 (relative) for dipolarophile $H_2C{=}CH{-}R$		
	R = alkyl	$-C_6H_5$	$-CO_2alk$
$C_6H_5{-}C{\equiv}\overset{\oplus}{N}{-}\overset{\ominus}{N}{-}C_6H_5$ (benzene, 80 °C) [24]	0.30	3.2	100
$C_6H_5{-}C{\equiv}\overset{\oplus}{N}{-}\overset{\ominus}{O}$ (ether, 20 °C) [25]	3.9	14	100
$N{\equiv}\overset{\oplus}{N}\ \overset{\ominus}{C}(C_6H_5)_2$ (DMF, 40 °C) [7]	0.01	0.2	100
$N{\equiv}\overset{\oplus}{N}\ \overset{\ominus}{N}{-}C_6H_5$ (CCl_4, 25 °C) [26]	2.4	4.1	100
 (chlorobenzene, 80 °C) [22]	1.8	5.1	100
 (*p*-cymene, 140 °C) [23]	5.8	8.0	100
 (toluene, 120 °C) [12]	0.67	3.0	100

Ordinary olefins react so sluggishly that their very small rate constants cannot be measured satisfactorily in all cases. The aromatic nucleus in styrene accelerates the rate 1.5- to 20-fold. The activating influence of a neighboring ketone group, a carboxylic ester, or a nitrile function is considerably greater. The rate constants for acrylic ester exceed those for nonconjugated olefins by one to four orders of magnitude.

Addition of a 1,3-dipole onto a double bond saturates the latter so that it can no longer participate in conjugation. The loss of conjugation energy reduces the exothermicity of the cycloaddition onto a conjugated double bond compared with that of an isolated one. How, then, does conjugation bring about a reduction of the activation barrier?

One important reason is the stabilization of partial charges, or possibly even of a partial radical character of the transition state involved in the 1,3-dipolar addition. The term "concerted addition" is not to be taken to imply that the two new σ-bonds form in the transition state to exactly the same extent. This "marching-in-step" principle is merely a limiting case. Normally the two bonds begin to form simultaneously but are developed to different extents in the activation configuration. Thus, if the closure of one bond occurs somewhat more rapidly than that of the other, then one center of the dipolarophile becomes the carrier of a partial negative or positive charge (or of a partial radical character), as the case may be. When neighboring substituents are present, they can take over and distribute such partial charges, which results in a reduction of the overall energy level.

The decrease in electron density of the double bond under the influence of a phenyl or alkoxycarbonyl residue cannot, however, be the only controlling factor, for chlorinated or fluorinated alkenes are especially poor dipolarophiles. Thus, without discussing all of the available experimental material, it may be suggested that yet another factor, namely polarizability, contributes to the high dipolarophilic nature of conjugated systems. The so-called exaltation of the molar refraction of conjugated systems demonstrates the magnitude of a special contribution to polarizability in such cases [27]. The Kerr effect offers convincing evidence that the additional polarizability of conjugated systems is localized in the π-electron cloud. This increased mobility of the bonding electrons should correspond to an enhanced tendency to enter into cyclic electron shifts.

When one intends to determine the optimum electron density at the reaction site, a substituted phenyl compound is used so that the effect of nuclear substituents on the rate constant can be measured. The evaluation of the data by means of the well-known Hammett equation yields the ρ-value specific to the reaction; the sign and magnitude of ρ indicate whether and to what extent the activation process requires a supply or withdrawal of electrons [28].

[24] *G. Wallbillich* and *E. Spindler*, unpublished results, Universität München, 1961/62.

[25] *W. Mack* and *E. Kudera*, unpublished results, Universität München, 1960/61.

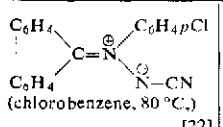
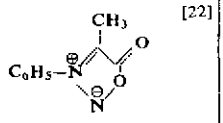
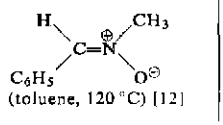
[26] *L. Möbius*, unpublished results, Universität München, 1962.

[27] Cf. the Table in *C. K. Ingold:* Structure and Mechanism. G. Bell, London 1953, pp. 125–137; *W. Hückel:* Theoretische Grundlagen der Organischen Chemie. 8th Edit., Akademische Verlagsgesellschaft, Leipzig 1956, Vol. II, pp. 181–205.

[28] *L. P. Hammett:* Physical Organic Chemistry. McGraw-Hill, New York 1940, p. 184; *H. H. Jaffé*, Chem. Reviews *53*, 191 (1953).

We have measured the rates of addition of various 1,3-dipoles onto *p*-substituted styrenes (some examples in Table 6). The rate depends only slightly on the nature of the *p*-substituent, attaining a factor of 6 with *C*-phenyl-*N*-methylnitrone. It is only in this case that the Hammett equation is satisfied with a value of $\rho = +0.83$.

Table 6. Rate constants for 1,3-dipolar cycloadditions onto styrene and its *p*-substituted derivatives.

1,3-Dipole (solvent, temperature)	$k_2 \times 10^4$ [l/mole/sec] for *p*-$RC_6H_4CH{=}CH_2$				
	R=CH_3O	CH_3	H	Cl	NO_2
 (chlorobenzene, 80 °C) [22]	4.4		2.4		5.6
 (*p*-cymene, 140 °C) [23]	2.5	1.4	2.5	2.9	
 (toluene, 120 °C) [12]	0.87	0.93	1.17	2.7	5.1

The dipolarophilic character of the C≡C triple bond is similar in magnitude to that of the C=C double bond. Table 7 gives a comparison of the rate constants for styrene and phenylacetylene, as well as for acrylic and propiolic esters. Aromatic pyrazoles, isoxazoles, and 1,2,3-triazoles result in the additions of dipolarophilic triple bonds onto diphenyl(nitrile imine), benzonitrile-*N*-oxide, and phenyl azide, respectively, but not by addition onto the other 1,3-dipoles of Table 7. It is remarkable that the reactions leading to aromatic rings do not proceed at a faster rate. Evidently, the transition state of the cycloaddition does not profit from the aromatic resonance of the product. This surprising phenomenon will be discussed further below.

Table 7. Comparison of rate constants for 1,3-dipolar cycloadditions onto double and triple CC bonds.

1,3-Dipole	$k_2(H_2C{=}CH{-}C_6H_5)$ / $k_2(HC{\equiv}C{-}C_6H_5)$	$k_2(H_2C{=}CH{-}COOR)$ / $k_2(HC{\equiv}C{-}COOR)$
Diphenyl(nitrile imine) (80 °C) [24]	12	8.5
Benzonitrile oxide (20 °C) [25]	9.2	5.7
Diphenyldiazomethane (40 °C) [7]	1.2	0.67
Phenyl azide (25 °C) [21, 26]	1.4	0.95
Azomethine imine *(5)* (80 °C) [22]	0.64	0.22
N-Phenyl-*C*-methylsydnone (140 °C) [23]	1.4	0.38

The high dipolarophilic activity of angularly strained double bonds, such as those in *trans*-cyclooctene or in bicyclo[2,2,1]heptene and its derivatives, has already been mentioned. The rate of reaction of norbornene with nitrilium and diazonium betaines is 24–99 times faster than that of cyclopentene. The highest value is attained with phenyl azide (Table 8). Remarkably, this advantage vanishes in the case of 1,3-dipoles "without a double bond" [1]. With azomethine imines and nitrones, the ratio k_2(norbornene) / k_2(cyclopentene) is only 0.13–6.0; this phenomenon is as yet unexplained.

There are differences as well as similarities in the activity series. The ratio of the rate constants of ethyl

Table 8. Ratios of dipolarophilic activities toward nitrilium and diazonium betaines.

1,3-Dipole	k_2 (norbornene) / k_2 (cyclopentene)	k_2 (ethyl acrylate) / k_2 (norbornene)
Diphenyl(nitrile imine) (80 °C) [24]	24	15
Benzonitrile oxide (20 °C) [25]	91	0.68
Diphenyldiazomethane (40 °C) [7]	30	244
Phenyl azide (25 °C) [21, 26]	99	0.052

acrylate and norbornene (Table 8) might perhaps be taken as a quantitative measure of the affinity of 1,3-dipoles toward conjugated, electron-attracting substituents in the dipolarophile. Possibly this ratio increases with the magnitude of the partial negative charge which resides on the dipolarophile during the transition state of the 1,3-addition. Perhaps this is a key to the unravelling of the above-mentioned problem of the unequal rate of bond closure in the transition state.

2. Influence of Steric Factors

The greater the steric requirements of the transition state, the more sensitive the system is toward disturbances. The rates of concerted processes are often dramatically affected by steric factors. Table 9 shows the decrease in rate associated with the introduction of methyl groups into the α- or β-position of acrylic ester.

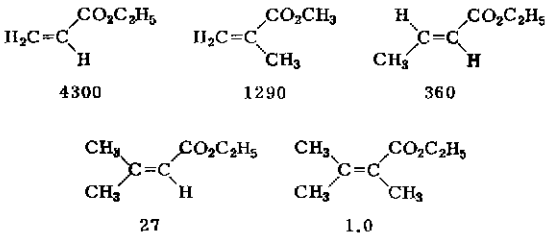
Table 9. Influence of methyl groups on the rate constants for additions onto acrylic ester.

1,3-Dipole	Relative k_2 values based on k_2 for acrylic ester = 100	
	$H_2C{=}\underset{\displaystyle CH_3}{\underset{\vert}{C}}{-}CO_2R$	$HC{=}\underset{\displaystyle CH_3}{\underset{\vert}{CH}}{-}CO_2R$
Diphenyl(nitrile imine) (85 °C) [24]	34	2.1
Benzonitrile oxide (20 °C) [25]	48	1.52
Diphenyldiazomethane (40 °C) [7]	7.2	0.35
Phenyl azide (25 °C) [26]	7.4	2.6
Azomethine imine *(5)* (80 °C) [22]	12	35
3,4-Dihydroisoquinoline-*N*-phenylimine (50 °C) [29]	3.5	0.9
C-Phenyl-*N*-methylnitrone (85 °C) [12]	30	8.4

The effect is greatest with diphenyldiazomethane; the rate constants for its cycloaddition onto methacrylic and crotonic esters are 14 and 280 times lower, respectively, than the values obtained for acrylic ester. This is in conformity with a phenomenon frequently observed in 1,3-dipolar additions, namely that steric hindrance in 1,1-disubstituted ethylenes is more pronounced than in the 1,2-disubstituted types. We suspect that the polar effect of the methyl group is less significant than its steric influence. The differing effects exerted by methyl groups, as apparent from the rate constants in Table 9, are caused by the varying spatial requirements of the 1,3-dipoles. Thus, with *C*-phenyl-*N*-methylnitrone, the decrease in the rate constant becomes rapid only when the acrylic ester is heavily substituted with methyl groups [12] (Scheme 3).

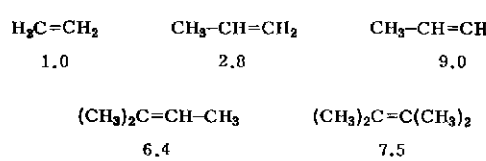
Ozone and nitrous oxide are the two 1,3-dipoles with the lowest steric requirements. With ozone, introduction of the first two methyl groups into ethylene is ac-

[29] *R. Schiffer*, unpublished results, Universität München, 1962.



Scheme 3. Rate constants $k_2 \times 10^6$ [l/mole/sec] in toluene at 120 °C for 1,3-dipolar addition of *C*-phenyl-*N*-methylnitrone onto methylated acrylic esters.

companied by an increase in reaction rate, while the third and fourth methyl groups induce a slight rate decrease [30] (Scheme 4).



Scheme 4. Relative values of k_2 for the addition of ozone onto methylated ethylenes at 20 °C in the gas phase [30].

These antagonistic tendencies of accelerating electronic and impeding steric effects are also encountered with phenylated ethylenes. Introduction of a second phenyl group into the α- or β-position of styrene is always accompanied by a decrease in reaction rate. Thus, the rate constant for 1,1-diphenylethylene is lower than that of styrene by the following factors: with diphenyl(nitrile imine) 15, with diphenyldiazomethane 8, and with *C*-phenyl-*N*-methylnitrone 12.

3. Rates of Addition to cis-trans Isomeric Alkenes

Kinetic studies of the stereoselective addition of 1,3-dipoles onto geometrically isomeric alkenes indicate a higher reactivity for the *trans*-isomers. Thus, *trans*-stilbene adds diphenyl(nitrile imine) 27 times faster than does *cis*-stilbene [24]. The ratios of the rate constants for additions onto dimethyl fumarate and maleate range from 58 to 2.9 (Table 10). Is this not surprising, because the addition of bromine or sulfite onto the energy-richer maleic ester is faster than that onto fumaric ester?

Table 10. Effect of configuration on the dipolarophilic activity of dimethyl ethylene-1,2-dicarboxylates.

1,3-Dipole	k_2 (fumaric ester) / k_2 (maleic ester)
Diphenyl(nitrile imine) (80 °C) [24]	36
Benzonitrile oxide (20 °C) [25]	58
Diphenyldiazomethane (40 °C) [31]	36
Phenyl azide (25 °C) [26]	25
Azomethine imine *(5)* (80 °C) [22]	5.2
C-Phenyl-*N*-methylnitrone (85 °C) [12]	2.9

cis-Stilbene and maleic ester both have angles of 120° at the sp^2-hybridized carbon atoms and show some overlapping of the van der Waals radii of their *cis*-substituents even in the ground state. The result is a steric hindrance of resonance, which can be detected in the ultraviolet spectra of the *cis*- and *trans*-forms; the π-electron system can be coplanar only in the *trans*-form. The hindrance of mesomerism in the *cis*-isomer weakens the activating effect of the phenyl or carboxylic group in the cycloaddition.

However, there is a second factor of even greater importance. Comparison of Tables 9 and 10 shows that the rate constants for the reaction of maleic ester with 1,3-dipoles which are especially sensitive to steric hindrance in the dipolarophile are particularly much lower than the rate constants for the reaction with fumaric ester. During the concerted addition of a 1,3-dipole, *abc*, hybridization of the central carbon atoms of the olefinic dipolarophile changes gradually from sp^2 to sp^3. Even though the CC distance is thus somewhat lengthened, the attendant shrinkage of the bond angle from 120 to 109° results in considerable compression of the van der Waals radii of the eclipsed *cis*-substituents as illustrated convincingly by the scale drawing (Figure 2). Thus, an increase in the van der Waals repulsion results during the activation process. This increase leads in turn to a higher activation energy for the cycloaddition to the *cis*-isomer, whereas the addition onto the *trans*-isomer is free from this disadvantage.

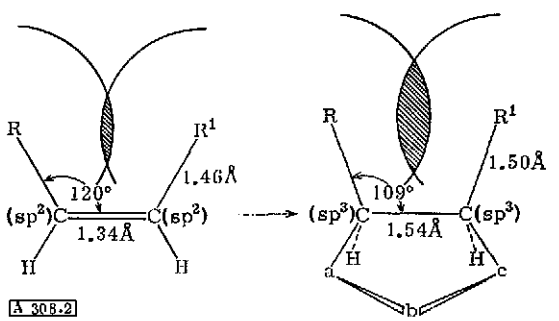
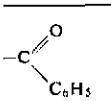
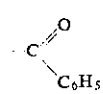
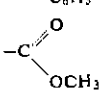
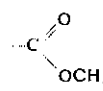
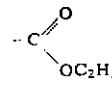


Fig. 2. Steric changes occurring during the cycloaddition of a 1,3-dipole, *abc*, to a *cis*-1,2-disubstituted ethylene.

If this explanation is correct, then the ratio of *trans*/*cis* rate factors should increase as the bulk of the substituents R colliding in the *cis*-configuration increases. This is indeed the case, as is confirmed by the rates of addition of diphenyldiazomethane [31] (Table 11). Thus, the bulky benzoyl residues of dibenzoylethylene cause the ratio to rise to 110, while in the case of ethyl crotonate,

Table 11. Ratios of rate constants for the addition of diphenyldiazomethane onto geometrically isomeric alkenes at 40 °C; R and R' are substituents on ethylene [31] (cf. Fig. 2).

R	R'	k_2 (*trans*) / k_2 (*cis*)
		110
		36
$-CH_3$		2.6

[30] *T. Vrbaski* and *R. J. Cvetanović*, Canad. J. Chem. *38*, 1053 (1960).

[31] *R. Huisgen, H. J. Sturm*, and *H. Wagenhofer*, Z. Naturforsch. *17b*, 202 (1962).

where the smaller methyl and ethoxycarbonyl groups interact, the *trans*-form reacts only 2.6 times faster. Incidentally, the same phenomenon has also been reported by *J. Sauer* [32] for the Diels-Alder synthesis. The ratio of the *trans/cis* rates offers an elegant and theoretically clear criterion for concerted additions leading to five- and six-membered rings.

4. Principle of Maximum Gain in σ-Bond Energy

Is there a universal activity sequence of dipolarophiles in the 1,3-cycloaddition? Unfortunately, a closer inspection of the results outlined above destroys any such illusions straight away. Instead, it is necessary to elaborate the specific sequence of dipolarophilic activity for each new 1,3-dipole.

A significant determining factor is reached by including dipolarophiles containing hetero-atoms in the comparison. The ability of such systems to undergo addition is often inferior to structurally analogous *C,C*-dipolarophiles; however, the highly polarizable C=S double bond frequently constitutes an exception. The kinetic data for the addition of diphenyl(nitrile imine) and benzonitrile oxide onto acetylene derivatives and the related nitriles may serve as an illustration. The ratios presented in Table 12 disclose the higher activity of the C C triple bond.

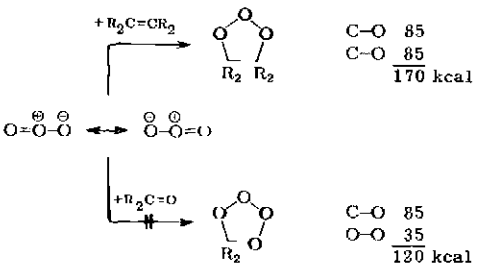
Table 12. Comparison of dipolarophilic activities of acetylenes and nitriles.

1,3-Dipole (solvent, temperature)	$k_2(C_6H_5-C\equiv CH)$ / $k_2(C_6H_5-C\equiv N)$	$k_2(HC\equiv C-COOR)$ / $k_2(N\equiv C-COOR)$
$C_6H_5-C\equiv\overset{\oplus}{N}-\overset{\ominus}{N}-C_6H_5$ (benzene, 80 °C) [24]	15	4.2
$C_6H_5-C\equiv\overset{\oplus}{N}-\overset{\ominus}{O}$ (ether, 20 °C) [25]	20	9.9

The superiority of the *C,C*-dipolarophile becomes even greater if, for example, benzaldehyde or glyoxylic ester are compared with styrene or acrylic ester. The 1,3-dipoles of Table 12 add onto carbonyl compounds only very slowly. The lower activity of the hetero-dipolarophiles is shown still clearer in their behavior towards phenyl azide, *i.e.* nitriles barely react, whereas aldehydes and ketones do not add at all. The two-step scheme presented on p. 634 would predict higher activity for hetero-dipolarophiles, since the oxygen or the nitrogen atoms present in position *d* of the intermediate *(9)* should readily assume a negative charge.

An explanation of numerous activity ratio data is supplied by the principle of maximum gain in σ-bond energy. Thus, the driving force behind the 1,3-dipolar addition is the stronger, the more the loss of π-bond energy in the reactants is overcompensated by the energy of the two new σ-bonds. A part of this σ-bond energy contributes already to the transition state of the concerted cycloaddition.

Thus, the 1,3-addition of ozone yields primary ozonides only with olefinic or aromatic C=C bonds whereas cycloadditions onto C=O or C=N double bonds are unknown. The reason is readily apparent. Two new C–O single bonds are closed in the addition to the alkene; this corresponds to a bond energy of 170 kcal. Addition



onto a carbonyl group would yield one C–O single bond and one O–O single bond; the attendant gain of only 120 kcal of σ-bond energy does not provide sufficient driving force for the cycloaddition since the reactants would have to sacrifice their π-bond energy. Of course, the activation configurations for the two ozone additions will not differ by this full amount of 50 kcal, but the difference will certainly constitute an appreciable fraction of this value.

The gain in σ-bond energy is perhaps the most important reason for the difference between the activity scales of the dienophiles and dipolarophiles. As an example, azodicarboxylic ester displays a very great readiness to add dienes at the N=N double bond; the gain in σ-bond energy associated with this process amounts to 146 kcal. In contrast, the addition of diphenyl(nitrile imine) or phenyl azide onto azodicarboxylic ester is sluggish. However, this is not surprising if we remember that these reactions are associated with σ-energy gains of only 112 and 78 kcal, respectively.

F. Orientation Phenomena

All unsymmetrically bonded dipolarophiles can add the 1,3-dipole in two directions, since with few exceptions 1,3-dipoles lack bond symmetry. To what extent can the orientation phenomena be explained, and the direction of the addition be correctly predicted?

1. In Dipolarophiles with Hetero-Atoms

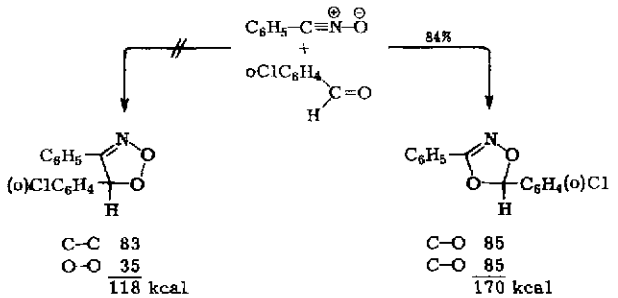
The nature of the new σ-bonds not only influences the activity series of dipolarophiles, but also determines the orientation. Dipolarophiles with multiple bonds including a hetero-atom usually add the dipole in only one of the two possible directions. Thus, the addition of benzonitrile-*N*-oxide onto aldehydes yields exclusively derivatives of the 1,3,4-dioxazole system [33]. The formation of the structurally isomeric heterocycle would involve a gain of σ-bond energy which is smaller by 52 kcal. In the addition of diphenyl(nitrile imine) onto azomethines [34], a difference in σ-bond energy of the

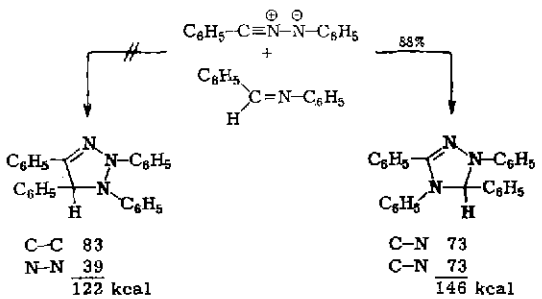
[32] *J. Sauer, H. Wiest*, and *A. Mielert*, Z. Naturforsch. *17b*, 203 (1962); *J. Sauer, D. Lang*, and *H. Wiest*, ibid. *17b*, 206 (1962).

[33] *R. Huisgen* and *W. Mack*, Tetrahedron Letters *1961*, 583.

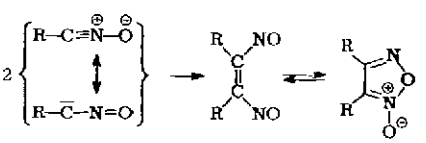
[34] *R. Huisgen, R. Grashey, M. Seidel*, and *H. Knupfer*, unpublished results, 1959/62.

products of 24 kcal is sufficient to direct the reaction entirely into the channel leading to Δ^2-1,2,4-triazolines. As already stressed above, the energy of the new σ-bonds becomes only partly (estimated at 20–40 % of the total) available in the transition state of the cycloaddition.

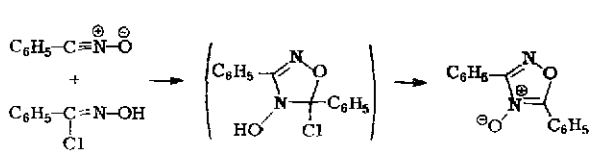




In contrast to the numerous cases in which the maximum gain in σ-bond energy dictates the direction of addition, there are a few exceptions of special interest. It is reasonable to postulate a change in mechanism for these cases. One example is the dimerization of nitrile oxides to form furoxans, whereby one C–C and one N–O bond are closed. A dynamic equilibrium between benzofuroxan and a modest concentration of *o*-dinitrosobenzene has been detected at room temperature [35]. The existence of this equilibrium suggests a two-step mechanism for furoxan formation: in the first step, the nitrile oxide, which can be represented by a nitrosocarbene structure, dimerizes to a dinitrosoethylene. This multistep path naturally no longer obeys the principle of maximum gain in σ-bond energy.



Benzonitrile oxide appears to add onto the C=N double bond of benzhydroxamoyl chloride in a "normal" fashion; in any event, spontaneous decomposition of the latter leads to the derivative *(19)* of the isomeric 1,2,4-oxadiazole [36], during the formation of which C–O and C–N single bonds are closed.



(19)

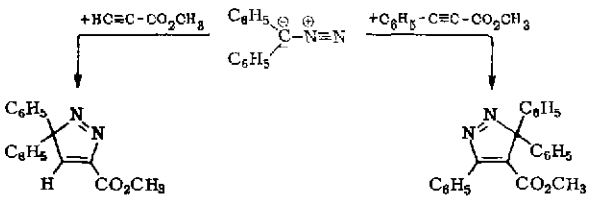
[35] *G. Englert*, Z. Naturforsch. *16b*, 413 (1961); *A. R. Katritzky, S. Oksne*, and *R. K. Harris*, Chem. and Ind. *1961*, 990; *P. Diehl, H. A. Christ*, and *F. B. Mallory*, Helv. chim. Acta *45*, 504 (1962).

[36] *H. Wieland*, Ber. dtsch. chem. Ges. *40*, 1667 (1907).

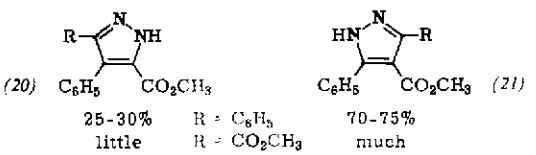
2. In Dipolarophiles of the Alkene and Alkyne Series

With alkenes or alkynes as dipolarophiles, both directions of addition produce, of course, the same amount of σ-bond energy. The interplay of electronic and steric substituent effects – the latter usually being dominant – is responsible for the orientation here. The large amount of factual material on the subject may be illustrated with a few examples.

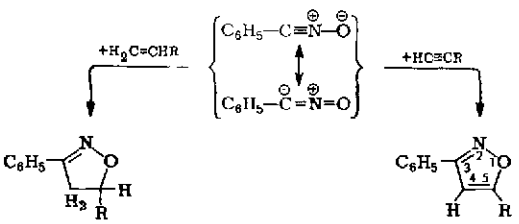
Diphenyldiazomethane adds onto propiolic ester in one direction only. This direction is favorable both from the steric and electronic points of view. The latter statement is based on the experimental evidence that the central carbon atom of the diazoalkane is more strongly nucleophilic than the outer nitrogen. In the case of phenylpropiolic ester, the direction of addition is reversed with respect to the carboxylic ester group [37].



The spatial requirements of the phenyl residue are greater than those of the methoxycarbonyl group and the steric effect is dominant in this addition. This is suggested by experiments with diazoalkanes in which the steric demand of the central carbon is lower. With phenyldiazomethane or diazoacetic ester, a mixture of products resulting from both directions of addition is obtained, although the sterically favored isomer *(21)* is the principal one [37].



Benzonitrile-*N*-oxide combines with all monosubstituted ethylenes or acetylenes to form 5-substituted 3-phenylisoxazolines or -isoxazoles; the substituent may be an alkyl or an aryl residue, and have either an electron-attracting or an electron-donating character [38]. Attachment of the dipolarophilic carbon of greater spatial

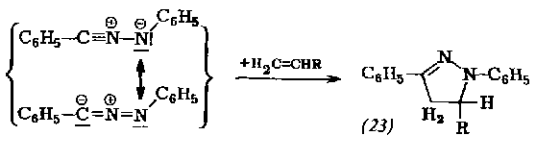


[37] *E. Buchner* and *M. Fritsch*, Ber. dtsch. chem. Ges. *26*, 256 (1893); *E. Buchner* and *W. Behaghel*, ibid. *27*, 869 (1894); *R. Hüttel, J. Riedl, H. Martin*, and *K. Franke*, Chem. Ber. *93*, 1425 (1960).

[38] *A. Quilico* and *G. Speroni*, Gazz. chim. ital. *76*, 148 (1946); *G. Stagno d'Alcontres* and *P. Grünanger*, ibid. *80*, 741, 831 (1950); *G. Stagno d'Alcontres*, ibid. *82*, 627 (1952); *P. Grünanger*, ibid. *84*, 359 (1954); *P. Grünanger* and *M. R. Langella*, ibid. *89*, 1784 (1959); *G. Gaudiano, A. Quilico*, and *A. Ricca*, Tetrahedron *7*, 24 (1959).

requirements with the oxygen of the nitrile oxide is undoubtedly the sterically more favored route.

If the anionic oxygen of benzonitrile-*N*-oxide is replaced by an anilino residue, the dipole becomes diphenyl(nitrile imine), which obeys an exactly analogous orientation rule. Butadiene, styrene, acrylic ester, acrylonitrile and even the isolated double bond of n-heptene yield the 5-substituted Δ^2-pyrazolines *(23)* with this 1,3-dipole; no product of the reverse orientation was detected in even a single case [16]. Can this still be a matter of steric influence?

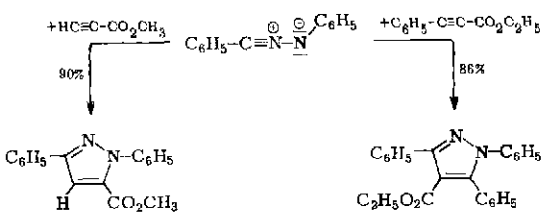


(22) *(23)*

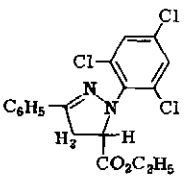
R = C_5H_{11} 85% R = C_6H_5 88%
R = $CH{=}CH_2$ 94% R = CN 85%
R = $CO_2C_2H_5$ 85%

As will be shown later, nitrile imines can attain the mesomerism characterized by formula *(22)* only if the geometry of the ground state corresponds to that of the nitrilium resonance structure, with sp-hybridization at the central carbon atom. In this case, the nitrogen permits the approach of a dipolarophilic center of a higher steric requirement noticeably more easily than does the nitrile imine carbon. Thus, even though the mesomeric effect of the ethoxycarbonyl group in acrylic ester should promote an addition resulting in the 4-substituted pyrazoline, the commanding steric influence determines the orientation.

The specificity with which even monosubstituted acetylenes add diphenyl(nitrile imine) to yield 5-substituted 1,3-diphenylpyrazoles is astonishing [16]. Comparison of the results obtained with propiolic ester and with phenylpropiolic ester is still in agreement with this tentative assumption of steric control. Also here, as with diphenyldiazomethane, reversal of the direction of addition occurs with respect to the ester function. The reaction path resulting in the appearance of the phenyl at the 5-position is once again the sterically more favorable route.



It should be expected that the steric preference for addition onto the nitrile imine nitrogen would vanish if the *N*-phenyl residue were to be encumbered with bulky substituents. This, however, is not the case, as is shown by the adducts *(24)* and *(25)* obtained from *C*-phenyl-*N*-trihalogenophenyl(nitrile imine) with acrylic ester and 1,1-diphenylethylene, respectively [39]. It is true that the trihalophenyl residue is twisted out of the coplanarity with the nitrile imine bond system; however, the strictness with which the same orientation rule is followed is really remarkable and casts doubt on a purely steric interpretation.



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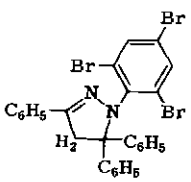
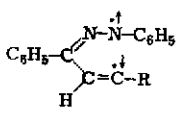


(25)

It should also be mentioned briefly that a mechanism assuming the existence of a spin-coupled biradical intermediate fails to offer an unequivocal interpretation of the orientation phenomena. The unidirectional addition to monosubstituted ethylenes and acetylenes can admittedly be understood in terms of the intermediate *(26)*, since alkyl, aryl, and carboxylic ester groups are able to stabilize the radical when present in position R. However, with phenylpropiolic ester, the actual orientation does not correspond to that expected from such an intermediate, since the kinetic data of Table 5 leave no doubt that the carboxylic ester group is far more strongly activating than phenyl.



(26)

The interplay of the factors determining orientation is thus somewhat unclear in many cases. This, incidentally, is also true of the influence of substituents on the direction of Diels-Alder addition [40].

G. Kinetics and Structural Variation of the 1,3-Dipole

It has already been shown qualitatively (Table 1) that the ability of substituted diazomethanes to undergo cycloaddition decreases with their resonance stabilization in the ground state. When the mesomeric substituent effects of the 1,3-dipole are compared with those in the cyclic adduct, one often arrives at a reasonable correlation with the reaction rates. However, the few observations available at present are no substitute for a systematic investigation.

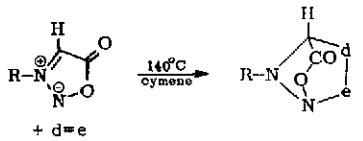
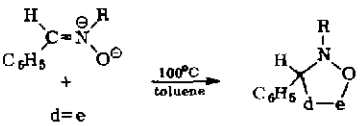
Although the addition of the dipolarophile usually results in higher coordination numbers at the charge centers of the 1,3-dipole, in certain situations, the cycloaddition produces release of mesomeric effects. Thus, the octet structures of the sydnones or nitrones reveal that the mesomeric electron-attracting effect of any substituent R at the immonium nitrogen is suppressed; however, in the adduct, the unshared electron pair at the now trivalent nitrogen becomes available for resonance with R. The gain in resonance energy thus increases the driving force of the cycloaddition. Naturally this effect is proportional to the ability of the aromatic nucleus to take up electrons.

In 1,3-dipoles "without a double bond" [1], the configuration is of primary importance. In *C*-phenyl-*N*-methylnitrone, the organic residues are *trans* to the C - N double bond. Fixation of the *cis*-configuration in dihydroisoquinoline-*N*-oxide by the cyclic structure

[39] *V. Weberndörfer*, unpublished results, Universität München, 1961/62.

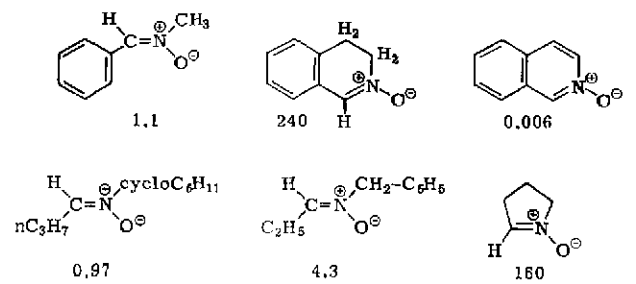
[40] *K. Alder* and *M. Schuhmacher*, Fortschr. Chem. org. Naturst. *10*, 21 (1953).

Table 13. Relative rate constants for the reaction of *N*-substituted sydnones with ethyl phenylpropiolate [23], and of *N*-substituted *C*-phenylnitrones with ethyl crotonate [12].

1,3-Addition	R	k_2(rel.)
	$C_6H_5-CH_2-$	3.8
	$pCH_3O-C_6H_4-$	7.2
	C_6H_5-	=10.0
	$pCl-C_6H_4-$	18.2
	CH_3-	2.0
	$pCH_3O-C_6H_4-$	7.1
	C_6H_5-	=10.0
	$pCl-C_6H_4-$	15.8

results in a 200-fold increase in the rate of 1,3-cycloaddition (Table 14). Dialkylnitrones and Δ^1-pyrroline-*N*-oxide show similar behavior. The rate constant for the addition of isoquinoline-*N*-oxide is 40000 times smaller than that of the 3,4-dihydro derivative because the aromatic pyridine mesomerism has to be sacrificed during the cycloaddition.

Table 14. Rate constants $k_2 \times 10^5$ [liters/mole/sec] for the addition of some nitrones onto ethyl crotonate in toluene at 100 °C [12].



Polar substituent effects have relatively little influence on the specific rate of addition of a 1,3-dipole. So far we know of only one surprising exception: this occurs with the aromatic azides, whose special tendency to add onto electron-rich double bonds has already been mentioned [1]. *p*-Nitrophenyl azide adds onto norbornene eight times faster than does *p*-methoxyphenyl azide (Table 15). However, the aromatic azide displays opposing substituent effects depending on whether it adds onto an olefinic dipolarophile of higher or lower electron density. In the addition onto maleic anhydride (which has an electron-deficient double bond) *p*-methoxyphenyl azide exceeds the *p*-nitro compound by a factor of sixteen. The order of magnitude is especially noteworthy with the electron-rich double bond of pyrrolidinocyclohexene (an enamine): the Hammett ρ-value rises here to +2.6.

Table 15. Rate constants for 1,3-additions of organic azides onto olefinic dipolarophiles in benzene at 25 °C [21, 26].

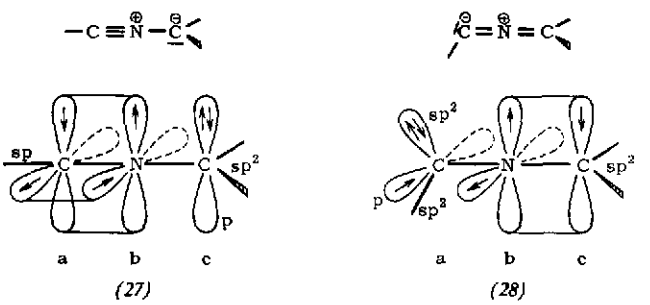
$R-\overset{\ominus}{N}-\overset{\oplus}{N}\equiv N$ R =	$k_2 \times 10^7$ [liters/mole/sec] for maleic anhydride	*N*-phenylmaleimide	norbornene	pyrrolidinocyclohexene
$pNO_2-C_6H_4-$	1.3	11	1530	1480000
C_6H_5-	7.2	28	254	9930
$pCH_3O-C_6H_4-$	21	67	187	3400
ρ (Hammett)	−1.2	−0.7	+0.8	+2.6
$C_6H_5-CH_2-$	53	95	22	25

It is noteworthy that the rate of addition of benzyl azide is scarcely affected by the electron density of the dipolarophilic double bond. Further investigation is needed to show whether a change in mechanism is involved in this case, *e.g.* a transition from a "true" 1,3-dipolar addition to a process involving a zwitterionic intermediate.

H. Molecular Orbital Considerations

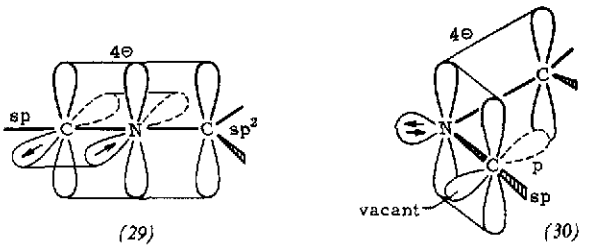
The resonance of the two octet formulae of 1,3-dipoles "with a double bond" is no longer self-evident if the orbital hybridization of the two octet structures is

considered separately. Taking the nitrile ylides as a model system, it can be seen that accommodation of the lone electron pair at carbon atom *a* of formula *(28)* in an sp^2-orbital is energetically favored over that in a p-orbital. This should result in a bending of the bond system at carbon atom *a*, compared with the linear sp-hybridized σ-system of *(27)*.



(27) *(28)*

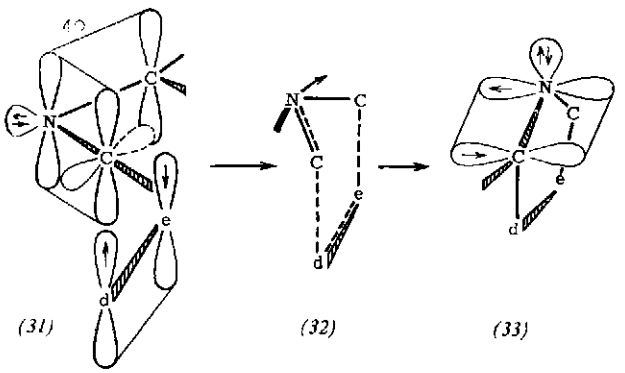
In terms of the MO theory, mesomerism of the structures above is equivalent to saying that delocalization of four π-electrons in the three p-orbitals of the plane of the paper in formula *(29)* takes place. This can be achieved only in configuration *(27)* of the σ-bond system. To a first approximation, the delocalization energy in *(29)* is that of the allyl anion, which amounts in the LCAO treatment to 0.82 β, where β is the resonance integral [41]. It may be assumed that this gain in energy is larger than the loss associated with the establishment of sp-hybridization at carbon atom *a* in *(28)*.



(29) *(30)*

[41] Cf. *A. Streitwieser:* Molecular Orbital Theory. Wiley, New York 1961, p. 40.

During the activation process, the linear bond system *a-b-c* of the 1,3-dipole must necessarily bend in order to place centers *a* and *c* in contact with the π-bond system of the dipolarophile. How much energy does it take to achieve the transition from *(29)* to *(30)*, during which the π-bond perpendicular to the plane of the paper disappears? An LCAO calculation by *J. D. Roberts* [42] for the azide system – in which the relationships are simpler because of the identity of atoms *a*, *b*, and *c* – has pointed out that a loss of less than 1 β is involved in bending the linear configuration to an angle of 120°; the loss of π-bond energy is partly compensated by a gain in energy resulting from rehybridization and accommodation of a lone pair of electrons in an orbital of high s-character. The resonance energy of the "allyl anion" is not disturbed by the bending.



(31) *(32)* *(33)*

It is highly probable that the 1,3-dipole and dipolarophile *d=e* orient themselves during the formation of the activated complex in the fashion shown in *(31)*. This implies that the "allyl anion" orbitals at centers *a* and *c* interact with the π-bond of the dipolarophile. The gradual transformation of the p-orbitals into sp^2- or sp^3-orbitals of the new σ-bonds is accompanied by an interesting change in configuration. The nitrogen is moved upwards (in the simplified picture *(32)* of the transition state, the path is indicated by an arrow) until it reaches the plane of the remaining four centers in adduct *(33)*. In the course of this continuous transition, the orbital of the lone electron pair at the nitrogen in *(31)* attains p-character; the π-bond of the product originates from this pair of electrons. Of the four electrons of the "allyl anion" orbital, only two are utilized in the creation of the new σ-bonds; the other two appear as an unshared pair of electrons on the nitrogen in the product *(33)*. The orbital concerned in *(33)* is to be considered as the remainder of the "allyl anion" system.

The C=N double bond of the adduct is not that of the angled 1,3-dipole in *(31)*; this is a significant phenomenon which did not come to light by the simple valence bond notation:

Rather, the original delocalized π-bond of *(31)* disappears during the progress of the reaction while a new π-bond is formed. This now explains why the rates at which nitrile imines, nitrile oxides, or azides add to triply bonded dipolarophiles do not profit from the aromatic resonance of the product (Table 7). The new p-orbitals, which later become part of the aromatic π-electron cloud, are still insufficiently developed in the transition state. Moreover, the rapid decrease in π-interaction with increasing distance contributes to the absence of any aromatic resonance in *(32)*; in the transition state, the new σ-bonds are still quite long.

It may be a safe assumption that the transition state *(32)*, and hence the system at the peak of the activation barrier, is geometrically closer to the oriented complex *(31)* of the components than to the adduct *(33)*. Generally, the transition state in exothermic reactions resembles more the starting material than the product [43]. In this particular case, the entire loss of activation entropy has already been achieved on orienting the components into configuration *(31)*; it has been stressed on p. 637 that decrease in entropy accounts for a considerable part of the free energy of activation.

1,3-Dipoles "without a double bond" are already bent in the ground state; thus, there is no problem of initial bending here. All of these 1,3-dipoles are capable of forming a delocalized 4-electron system of the allyl anion type in a manner similar to that outlined above, so that the picture given for the course of cycloaddition holds here without limitation. It is clear by now that the terminology "biradical" or "ionic" cannot be applied to this mechanism.

We shall not discuss here an alternative description of the concerted addition which postulates that the five centers are aligned within the plane of the ring produced during the transition state. There is evidence against such a geometry of the activated configuration, *e.g.* with cyclic 1,3-dipoles such as those of the sydnones, the dipolarophile must necessarily approach at a right angle to the *a-b-c* plane of the 1,3-dipole.

The tendency to explain new reactions in the light of theoretical principles even at an early stage is undoubtedly greater today than ever before. If each individual experimental result is thought of as one stone in a mosaic, then many of these are needed before one is cognizant of the picture. The temptation is strong to start interpreting the picture even before the entire array of the mosaic stones is unveiled. It is possible, then, that future studies of 1,3-dipolar cycloadditions will bring to light further new colors and contours.

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[42] *J. D. Roberts*, Chem. Ber. *94*, 273 (1961).
[43] *G. S. Hammond*, J. Amer. chem. Soc. 77, 334 (1955).

New Developments in the Chemistry of Polyphosphanes

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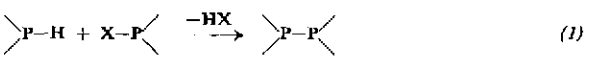
Dedicated to Prof. Dr. Karl Winnacker on the occasion of his 60th birthday

While silicon and sulfur, which are situated to the left and to the right of phosphorus in the periodic table, form numerous chain and cyclic Si–Si and S–S-compounds with varying numbers of members, until recently the polyphosphane chemistry has been limited to the two-membered compound diphosphane P_2H_4 and its derivatives. A number of results obtained in studies on polyphosphanes carried out in recent years will therefore be discussed, which, together with some more recent work by other authors, have led to an expansion of our knowledge of the preparation and properties of straight and branched-chain as well as of cyclic and polycyclic –P–P-systems.

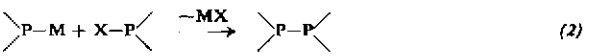
There are three principal ways in which P–P bonds may be formed:

1. by condensation of phosphanes with halogenophosphanes in the presence of a binding agent for the hydrogen halide such as NR_3



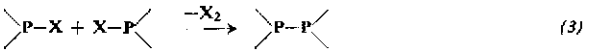
(1)

2. by reaction of alkali metal phosphanes with halogenophosphanes



(2)

3. by dehalogenation of halogenophosphanes by halogen-binding metals such as Hg.



(3)

As the following pages show, all three methods are suitable for the preparation of polyphosphanes.

I. Preparation of Phenyl Derivatives of a Triphosphane P_3H_5 by Condensation of Phenylhalogenophosphanes $PhPX_2$ with Phenylphosphanes Ph_2PH and $PhPH_2$ [*]

Condensation of phosphanes with halogenophosphanes according to Equation *(1)* is a well-known method that is frequently used for the synthesis of P–P-compounds. Thus, tetraphenyldiphosphane is formed from diphenylphosphane and diphenylchlorophosphane at 100 °C in ligroin [3,4] according to

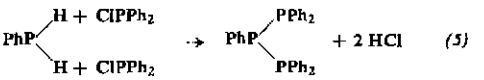
$$Ph_2PH + ClPPh_2 \rightarrow Ph_2P{-}PPh_2 + HCl \qquad (4)$$

It therefore seemed logical to attempt to obtain triphosphanes P_3R_5 in an analogous manner.

In this Section I, we shall describe two triphosphanes that were obtained by the condensation reaction *(1)*, *viz.* pentaphenyltriphosphane and triphenyltriphosphane. Section II will deal with a third triphosphane, *viz.* pentaethyltriphosphane.

1. Pentaphenyltriphosphane $PhP(PPh_2)_2$

Kuchen and Buchwald [4] had previously attempted to synthetize a pentaphenyltriphosphane by condensation of diphenylchlorophosphane with phenylphosphane in a molar ratio of 2:1 in boiling toluene at 110 °C according to the equation:



(5)

However, they obtained instead a mixture of tetraphenylcyclotetraphosphane and tetraphenyldiphosphane, from which they concluded that pentaphenyltriphosphane is not particularly stable and disproportionates at elevated temperatures to P(I) and P(II) compounds according to

$$PhP(PPh_2)_2 \rightarrow {}^1/_4\,(PhP)_4 + (PPh_2)_2 \qquad (6)$$

In order to achieve condensation according to *(1)* at lower temperatures and thereby to prevent the onset of the disporportionation reaction *(6)*, we used a reaction mixture of 2 moles of Ph_2PH and 1 mole of $PhPCl_2$, instead of the 2 moles of Ph_2PCl and 1 mole of $PhPH_2$ used in Equation *(5)*. The reactivity of the chlorine

[*] Throughout this article, Ph = C_6H_5, Me = CH_3, and Et = C_2H_5.

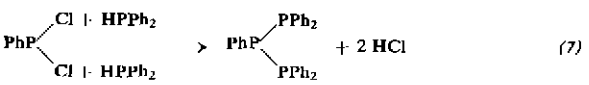
[1] *M. van Ghemen:* "Zur Kenntnis ketten- und ringförmiger Oligophosphane" [Chain and Cyclic Oligophosphanes], Diploma Thesis, Universität München, 1960; "Zur Kenntnis organosubstituierter Oligophosphane" [Organo-Substituted Oligophosphanes], Ph.D. Thesis, Universität München, 1962.

[2] *G. Müller-Schiedmayer:* "Über die Umsetzung von Phosphorhalogeniden mit Metallhydriden" [The Reaction of Phosphorus Halides with Metal Hydrides], Diploma Thesis, Universität München, 1958.

[3] *C. Dörken*, Ber. dtsch. chem. Ges. *21*, 1505 (1888).

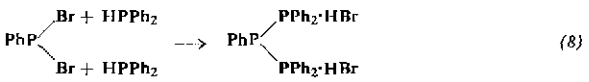
[4] *W. Kuchen* and *H. Buchwald*, Chem. Ber. *91*, 2871 (1958).

atoms in $PhPCl_2$ is greater than that of the Cl in Ph_2PCl, so that there was a possibility that condensation according to



could occur even at room temperature. However, when a frozen solution in ether of 2 moles of Ph_2PH and 1 mole of $PhPCl_2$ was melted and brought to room temperature, no condensation corresponding to Equation *(7)* occurred.

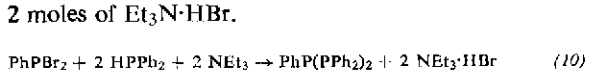
For this reason, we turned to the still more reactive bromine compound, $PhPBr_2$, which – as a preliminary experiment showed – reacts with Ph_2PH at room temperature in a strongly exothermic reaction. When a frozen [*] ether solution of 2 moles of Ph_2PH and 1 mole of $PhPBr_2$ is slowly heated to −10 °C *in vacuo*, colorless $P_3Ph_5 \cdot 2HBr$ precipitates without evolution of HBr. Thus, rather than producing free pentaphenyltriphosphane, the reaction forms the hydrobromide:



In this reaction, the hydrogen halide, formed analogously to that in the condensation reaction *(7)*, adds onto the Lewis base P_3Ph_5 to form the salt *(9)*.

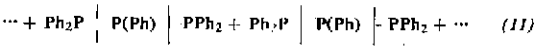
As expected, this salt is insoluble in ether, petroleum ether, and benzene. Because of its P–P bonds, it has strong reducing properties, *e.g.* it converts concentrated H_2SO_4 into SO_2 and precipitates metallic Ag from aqueous $AgNO_3$. The hydrogen bromide in the quaternary salt is given off only slowly at room temperature, even *in vacuo*. On the other hand, it reacts exothermically with triethylamine to form $Et_3N \cdot HBr$. Also, it decomposes on heating to 60 °C and deliquesces on brief exposure in air.

Thus, to obtain free pentaphenyltriphosphane, it is necessary to carry out reaction *(8)* in the presence of an HBr acceptor, such as triethylamine. If a frozen solution in ether of 2 moles of Ph_2PH, 1 mole of $PhPBr_2$, and 2 moles of NEt_3 is melted in a bath at −30 °C and then heated to room temperature with stirring, an ether solution of P_3Ph_5 is obtained with precipitation of 2 moles of $Et_3N \cdot HBr$.



A yellowish solid residue remains on evaporation *in vacuo* of the ether from the filtrate. On recrystallization from an ether/petroleum ether mixture, colorless crystals with the analytical composition of P_3Ph_5 are obtained; these melt with decomposition when heated in a melting-point tube to above 70 °C (see below).

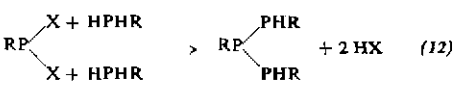
Pentaphenyltriphosphane is very soluble in benzene, toluene, chloroform, tetrahydrofuran, dioxane, and ether, slightly soluble in petroleum ether, and insoluble in methanol and water. Its molecular weight as determined by cryoscopy in benzene corresponds to the monomeric formula P_3Ph_5 (found 482; calculated 479). The compound is stable when stored under nitrogen; it deliquesces on brief exposure to air. It reduces concentrated HNO_3 in an explosive reaction, converts concentrated H_2SO_4 into SO_2, and precipitates black Ag from aqueous $AgNO_3$. Above 70 °C, P_3Ph_5 condenses to P_4Ph_4 with formation of P_2Ph_4 according to Equation *(6)*.



The infrared spectrum of P_3Ph_5 (NaCl prism; Nujol and Hostaflon) contains aromatic C–H vibration peaks at 3.3 μ and 13.6 μ, the characteristic C–H vibration peak for the phenyl radical at 14.5 μ, and a peak for the P–Ph vibration just below 7 μ.

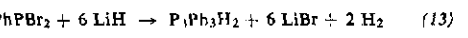
2. Triphenyltriphosphane $PhP(PHPh)_2$ [5]

The preparation of triphosphanes via the condensation shown in Equation *(1)* in the presence of an HX acceptor can be simplified in special cases. For example, triphosphanes of the type $P_3R_3H_2$ can be prepared according to the equation:

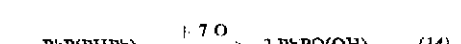


without adding the phosphane RPH_2 assuch. Here the organodihalogenophosphane itself may serve as the source of RPH_2. Lithium hydride, which is also the HX acceptor, is added to hydrogenate part of the RPX_2 to RPH_2; the latter then condenses with unreacted RPX_2 to form triorganyltriphosphanes according to Equation *(12)*.

For example, a solution in benzene of phenyldibromophosphane is added dropwise to a frozen suspension of excess lithium hydride in benzene. The mixture is melted *in vacuo* and the reaction takes place at the melting point of the benzene (5 °C). Hydrogen is evolved and triphenyltriphosphane is formed as follows:



The precipitate of LiBr is filtered off and the filtrate evaporated leaving the $P_3Ph_3H_2$ as a yellowish, crystalline substance (m.p. 113.5 °C) which is very sensitive to air. In solution in benzene it exists as the monomer (molecular weight: found 335, calculated 326). It is oxidized to phenylphosphonic acid (m.p. 160 °C) when heated together with dilute nitric acid.



When excess lithium aluminum hydride, which is a much faster hydrogenating agent, is substituted for the LiH in the reaction with phenyldihalogenophosphanes $PhPX_2$ in ether,

[*] To moderate the reaction.

[5] Experiments carried out by *G. Müller-Schiedmayer* [2]. All other polyphosphanes were investigated by *M. van Ghemen* [1].

the product is a phenylphosphane $PhPH_2$ ("phospha-aniline", m.p. −57 °C, b.p. 160 °C), instead of the triphosphane $P_3Ph_3H_2$, since the hydrogenation is so rapid that the rate of the condensation reaction *(12)* becomes insignificant in comparison [2, 6]. Similarly, on hydrogenation with excess $LiAlH_4$, diphenylhalogenophosphanes Ph_2PX are converted into diphenylphosphane, Ph_2PH, m.p. −14.5 °C, b.p. 280 °C [2, 4]. If the molar ratio in the condensation of $PhPH_2$ with $PhPX_2$ is 1:1 instead of 2:1, the product is a cyclotetraphosphane P_4Ph_4, instead of the triphosphane $P_3Ph_3H_2$ *(12)* [6].

$$2\ PhPH_2 + 2\ PhPX_2 \rightarrow [PhP]_4 + 4\ HX \qquad (15)$$

The triphenyltriphosphane we synthetized in 1957 via reaction *(13)* [2] and the tris(trifluoromethyl)triphosphane $P_3(CF_3)_3H_2$ obtained in the same year by *Mahler* and *Burg* [7] via hydrolysis of pentakis(trifluoromethyl)-cyclopentaphosphane $P_5(CF_3)_5$ were the first triphosphanes to be isolated. Other triphosphanes were prepared soon afterwards. For example, we prepared the pentaphenyltriphosphane described in Section I.1 via reactions *(5)* and *(18)* (see Section II.1) [1]; we also prepared pentaethyltriphosphane via reaction *(22)*, using $EtPCl_2$ and $LiPEt_2$ (Section II.2). *Nöth* and *Vetter* [8] obtained pentakis(dimethylamino)triphosphane $P_3(NMe_2)_5$ as a product of disproportionation of $P_2(NMe_2)_4$ resulting from dehalogenation of bis(dimethylamino)-chlorophosphane $(Me_2N)_2PCl$ with sodium.

II. Preparation of Organic Derivatives of a Triphosphane P_3H_5 via Condensation of Organohalogenophosphanes RPX_2 with Organoalkaliphosphanes $R_2PNa(Li)$

In Section I, we described the condensation of organohalogenophosphanes with organophosphanes according to:

$$RP(X + HPR_2)(X + HPR_2) \rightarrow RP(PR_2)(PR_2) + 2\ HX \qquad (16)$$

In order to obtain the free organotriphosphane bases P_3R_5H and to avoid formation of the respective phosphonium salts $[P_3R_5H_2]X_2$, the hydrogen halide liberated had to be scavenged with triethylamine or LiH.

This addition of an HX acceptor may be avoided if the organophosphanes are replaced by their alkali salts, *e.g.* R_2PNa, in accordance with Scheme *(2)*:

$$RP(X + NaPR_2)(X + NaPR_2) \rightarrow RP(PR_2)(PR_2) + 2\ NaX \qquad (17)$$

The alkali halide produced as by-product precipitates from the organic solvent and thus assures a quantitative action.

Here we shall discuss two triphosphanes obtained in this way, namely, pentaphenyltriphosphane and pentaethyltriphosphane.

[6] *W. Kuchen* and *H. Buchwald*, Chem. Ber. *91*, 2296 (1958).

[7] *W. Mahler* and *A. B. Burg*, J. Amer. chem. Soc. *79*, 251 (1957); *80*, 6161 (1958).

[8] *H. Nöth* and *H. J. Vetter*, Chem. Ber. *94*, 1505 (1961).

1. Pentaphenyltriphosphane $PhP(PPh_2)_2$

Sodium diphenylphosphane Ph_2PNa can be prepared from diphenylchlorophosphane and sodium in dioxane [9], is insoluble in ether and benzene, and retains varying amounts of dioxane on drying. An excess of Ph_2PNa was therefore used for the reaction with a solution in ether of $PhPCl_2$. The excess Ph_2PNa can be readily detected from the presence of yellow crystals. These and the insoluble NaCl formed can be readily separated by filtration from the soluble P_3Ph_5 obtained according to the reaction:

$$PhPCl_2 + 2\ NaPPh_2 \rightarrow PhP(PPh_2)_2 + 2\ NaCl \qquad (18)$$

Thus, a solution in ether of $PhPCl_2$ was added dropwise under nitrogen to a cold (−20 °C) suspension in ether of excess Ph_2PNa. The reaction mixture was then slowly heated to room temperature, when a precipitate of NaCl was formed according to Equation *(18)*. This precipitate and the excess Ph_2PNa were filtered off. The clear filtrate was concentrated, and pentaphenyltriphosphane precipitated out. The latter can be purified by recrystallization from a chloroform/petroleum ether mixture and is then obtained in the form of colorless crystals. Reaction *(18)* proceeds analogously in benzene; slow concentration of the solution at reduced pressure then yields particularly beautiful, colorless needles of P_3Ph_5.

The properties of the pentaphenyltriphosphane obtained from Ph_2PNa and $PhPCl_2$ in ether or benzene are exactly the same as those of the product obtained from Ph_2PH and $PhPBr_2$ in the presence of triethylamine (Section I.1). Again, the compound remains monomolecular on solution in benzene (molecular weight: found 473; calculated 479).

The preparation of P_3Ph_5 can be improved both qualitatively and quantitatively when tetrahydrofuran is used as solvent in reaction *(18)*. Ph_2PNa dissolves in tetrahydrofuran with a red color so that the stoichiometry of the reaction can be readily controlled [10]. Thus, if a solution of Ph_2PNa in tetrahydrofuran is added dropwise to a cold (−30 °C) solution in tetrahydrofuran of $PhPCl_2$ in a molar ratio of 2:1, a solution of P_3Ph_5 in tetrahydrofuran is formed, with simultaneous decolorization of the red solution and precipitation of NaCl. After heating to room temperature and removal of the solvent, a mixture of P_3Ph_5 and NaCl is obtained. The pentaphenyltriphosphane can be separated from the mixture in 96 % yield by extraction with benzene. The purity of the product is such that no further crystallization is necessary.

After the triphosphane P_3Ph_5 had thus become a readily accessible substance, its behavior with methyl iodide (MeI) was studied in order to obtain information on the strength of the P–P bonds in the molecule. Alkyl-substituted polyphosphanes, such as P_2R_4 [11] or P_4R_4 [12], add on MeI and thus form the stable salts $[P_2R_4Me]I$ or $[P_4R_4Me]I$. On the other hand, aryl-substituted phosphanes such as P_2Ph_4 [13] or P_4Ph_4 [14]

[9] *K. Issleib* and *A. Tzschach*, Chem. Ber. *92*, 1118 (1959).

[10] Determinations of the Ph_2PNa content of the tetrahydrofuran solutions were effected by titration of the sodium hydroxide formed on hydrolysis of a sample.

[11] *K. Issleib* and *W. Seidel*, Chem. Ber. *92*, 2681 (1959).

[12] *K. Issleib* and *B. Mitscherling*, Z. Naturforsch. *15b*, 267 (1960).

[13] *K. Issleib* and *A. Tzschach*, Chem. Ber. *92*, 1397 (1959); *H. Hoffmann*, *R. Grünewald*, and *L. Horner*, Chem. Ber. *93*, 861 (1960).

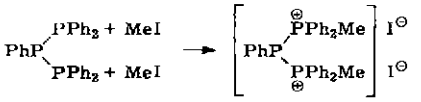
[14] *H. Hoffmann* and *R. Grünewald*, Chem. Ber. *94*, 186 (1961).

react with MeI with cleavage of P P bonds, for example, according to the equation:

$$P_2Ph_4 + 4\ MeI \rightarrow 2\ [PPh_2Me_2]I + I_2$$

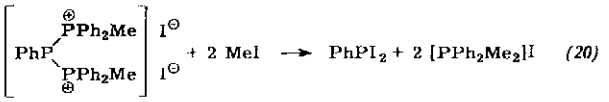
It was therefore of interest to find out whether P_3Ph_5 reacts with MeI with formation of a salt or with cleavage of the P–P bonds. If the latter reaction occured, we wanted to ascertain the mode of attack of the MeI, since two different types of phosphorus atoms are present in the P_3Ph_5 molecule.

When an excess of MeI was added to a solution of P_3Ph_5 in benzene and the mixture was left to stand for a short time, a precipitate of fine yellow needles of $[Ph_2PMe_2]I$ was obtained. All further precipitates were so strongly contaminated with iodine that isolation of any other individual cleavage product was very difficult. It can be concluded from our experiments that P_3Ph_5 first forms a phosphonium salt according to the equation:



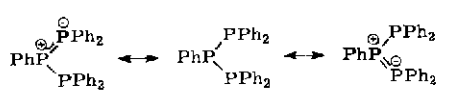
(19)

On the further reaction with MeI,



(20)

this intermediate salt is converted into $PhPI_2$ (+ 3 MeI → $[PhPMe_3]I$ + 2 I_2) and $[Ph_2PMe_2]I$. The fact that in reaction *(19)* the methyl groups add onto the two terminal phosphorus atoms – an addition corresponding to that of protons in the salt formation from P_3Ph_5 and HBr (Section I.1) – actually is contrary to what would be expected. The middle phosphorus atom carries only one electron-attracting phenyl group and therefore should be a stronger Lewis base than the terminal phosphorus atoms with their two phenyl substituents. Apparently the direction of addition is determined by the resonance of the P_3Ph_5, which can be formulated as follows:



(21)

This resonance reinforces the Lewis-basicity of the terminal P atoms and weakens that of the middle P atom. Furthermore, according to the Stuart model of P_3Ph_5, the middle P atom is so strongly shielded that access of a methyl group is made very difficult.

2. Pentaethyltriphosphane $EtP(PEt_2)_2$

After our successful synthesis of an aryl-substituted triphosphane P_3Ph_5 by reaction of $PhPCl_2$ with Ph_2PNa according to Equation *(18)*, an attempt was made to prepare an alkyl-substituted triphosphane, *viz.* pentaethyltriphosphane. Here the organoalkaliphosphane was Et_2PLi [9], which is more readily obtained (by treating diethylphosphane with butyl-lithium in ether) than the corresponding sodium compound Et_2PNa.

A solution of $EtPCl_2$ in ether was added dropwise *in vacuo* with stirring to a cold (–40 °C) solution-suspension of Et_2PLi in ether; the Et_2PLi was present in slight excess over the molar ratio $Et_2PLi:EtPCl_2 = 2:1$. An orange precipitate was obtained.

The ether, which was removed at –10 °C *in vacuo*, was free from halogen. This indicates that all the $EtPCl_2$ introduced was immediately consumed forming pentaethyltriphosphane according to the equation:

$$EtPCl_2 + 2\ LiPEt_2 \rightarrow EtP(PEt_2)_2 + 2\ LiCl \quad (22)$$

A moist, orange residue *(22)* was left after removal of the solvent; a colorless liquid F was then distilled off *in vacuo* at 95 °C, leaving a residue R.

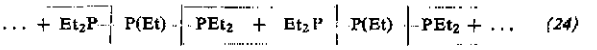
This residue R contained the small excess of Et_2PLi and a quantity of LiCl accounting for the total chloride introduced plus a red-brown polymeric organic phosphorus compound, which was insoluble in ordinary organic solvents, ignited spontaneously in air, and (in analogy to the decomposition *(6)* of P_3Ph_5 at elevated temperature) probably represented a product of disproportionation of P_3Et_5 of the composition $(PEt)_n$.

The colorless, halogen-free liquid F obtained as "distillate" was separated by a second distillation at room temperature *in vacuo* into a volatile and a nonvolatile component. Both of these ignited spontaneously in air. The volatile component was not homogeneous (as shown by its phosphorus content and molecular weight) and evidently consisted of a mixture of PEt_3 and P_2Et_4. The component nonvolatile at room temperature was the desired pentaethyltriphosphane, judging from its P, C, and H analyses and its molecular weight in benzene (found 240; calculated 238). The yield of this compound was 15 %, based on the $EtPCl_2$ used.

As the results obtained on working up the compound indicate, the low yield of P_3Et_5 can be attributed to its great tendency to disproportionate. In analogy to Equation *(6)*, the disproportionation leads in accordance with

$$EtP(PEt_2)_2 \rightarrow 1/n\ (EtP)_n + (PEt_2)_2 \quad (23)$$

to $(PEt)_n$ and $(PEt_2)_2$ (as well as to PEt_3):

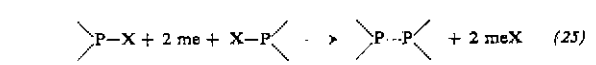


(24)

Pentaethyltriphosphane is an oily, colorless liquid, which oxidizes very readily in air with spontaneous ignition. Even traces of oxygen in repurified nitrogen are sufficient to cause turbidity in a sample that is stored under nitrogen. It is evident from these properties that the ethyl compound is considerably more reactive and more inclined to disproportionate than the phenyl compound.

III. Preparation of Organo Derivatives of a Cyclotetraphosphane P_4H_4 by Condensation of Organohalogenophosphanes RPX_2 by Means of Mercury

The synthesis of C–C bonds known in organic chemistry as the "Wurtz-Fittig reaction" has also found application in phosphorus chemistry, where it is used to interlink phosphorus atoms according to Scheme *(3)*, where me = one equivalent of a metal.



(25)

Thus, halogenophosphanes are dehalogenated by means of a metal. In the experiments already described in the literature, the metals principally used were alkali metals [8, 11], magnesium [15, 16], and mercury [7, 17].

Up to the present, only the reactions of halogenophosphanes with alkali metals have been thoroughly investigated. These reactions are often accompanied by an undesirable cleavage of the P–P bond by the alkali metal, with formation of an alkali phosphane [18]. Thus, sodium diphenylphosphane can be prepared directly from diphenylchlorophosphane and sodium in dioxan [9]. So far, dehalogenations with metallic magnesium were successful with phosphorus oxybromide $POBr_3$ and phosphorus thiobromide $PSBr_3$, whereby compounds of the formula $(PO)_x$ [15] and $(PS)_x$ [16] were formed.

Some preliminary experiments were carried out with solutions of organohalogenophosphanes $PhPX_2$ and Ph_2PX on the one hand, and the solid metals Mg, Zn, and Cu on the other. These studies showed that the reaction comes almost to a standstill after the formation of a crust of halide on the solid metallic surface, because the reaction is a heterogeneous reaction at the metal-solution interface.

In order to avoid these difficulties, we chose liquid mercury as the metallic reagent. The reactions of bis(trifluoromethyl)iodophosphane and trifluoromethyl-diiodophosphane with mercury at room temperature, which lead either to a tetrakis(trifluoromethyl)diphosphane [17] or to a mixture of tetrakis(trifluoromethyl)cyclotetraphosphane and pentakis(trifluoromethyl)cyclopentaphosphane [7], respectively, had by that time already been described in the literature.

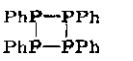
1. Preparation of Tetraphenylcyclotetraphosphane P_4Ph_4

An excess of mercury was added to a solution of phenyldibromophosphane in benzene and care was taken to obtain an intimate mixture of the reagents by continuous agitation with a magnetic stirrer. Since no change could be detected in the solution at room temperature, it was refluxed (80 °C). Soon, a precipitate of Hg_2Br_2 was formed which was gray on account of the excess mercury and which suggested that a reaction such as

$$n\ PhPBr_2 + 2\ n\ Hg \rightarrow (PhP)_n + n\ Hg_2Br_2 \qquad (26)$$

had taken place.

After a reaction period of six hours, the benzene solution contained no more halogen, indicating that reaction *(26)* was quantitative. The solution remaining after the Hg_2Br_2 and the excess Hg had been filtered off was then evaporated to dryness under reduced pressure; a solid yellowish substance was obtained and was purified by recrystallization from a benzene/petroleum ether mixture. Beautiful, colorless needles, m.p. 151 °C, were thus obtained in 91 % yield. Analysis and a molecular-weight determination in benzene (found 442; calculated 432) proved these to be the tetraphenylcyclotetraphosphane *(27)* described by *Kuchen* and *Buchwald* [6].



(27)

The infrared spectrum of the compound also agreed with the spectrum of the compound obtained by *Kuchen* and *Buchwald* by condensation of phenylphosphane with phenyldichlorophosphane in boiling ether.

$$2\ PhPH_2 + 2\ PhPCl_2 \rightarrow (PhP)_4 + 4\ HCl \qquad (28)$$

Thus, even though the parent substance of the phenyl derivative – *viz.* phosphorus(I) hydride – is a high polymer $(PH)_x$, its phenyl derivative $(PPh)_4$ is only tetrameric, probably because of steric reasons.

Condensation products of high molecular weight, *i.e.* $(PhP)_n$ with $n>4$, could not be obtained by reaction *(26)*. This fact does not, of course, preclude the possibility that such compounds are indeed formed, but then rearrange on prolonged heating of the benzene solution to the thermally more stable tetraphenylcyclotetraphospbane. Thus, *Reesor* and *Wright* [19] reported that under milder conditions the same reaction gave products with higher melting points (254 °C and 193 °C, respectively). On repeated melting, these were finally converted into a homogeneous substance with a m.p. of 148 °C. The authors attributed this change in m.p. to a rearrangement of high molecular-weight compounds $(PhP)_n$ into low molecular-weight entities.

Rings with a larger number of members were isolated in the case of the methyl [20] and the trifluoromethyl compounds [7] $(PMe)_5$ and $[P(CF_3)]_5$.

The reaction of $PhPBr_2$ with Hg in boiling benzene has made the tetraphenylcyclotetraphosphane a readily accessible substance [*]. This suggested the possibility of varying reaction *(26)*. An attempt was therefore made to replace the phenyldibromophosphane by the chloro compound. In this case, however, no precipitation of Hg_2Cl_2 occurred even after boiling a benzene solution for 6 hours with excess Hg. The $PhPCl_2$ reagent was recovered unaltered from the filtrate. This finding is in agreement with the generally known fact that the P–Cl bond is less reactive than the P–Br bond.

2. Reaction of Diphenylbromophosphane with Mercury

In order to determine whether the reactivity of the bromine in phenyldibromophosphane is lessened by the introduction of a second phenyl group, *i.e.* by using the diphenyl compound, diphenylbromophosphane was treated with mercury in boiling benzene.

$$2\ Ph_2PBr + 2\ Hg \rightarrow Ph_2P{-}PPh_2 + Hg_2Br_2 \qquad (29)$$

[15] *W. Kuchen* and *H. G. Beckers*, Angew. Chem. *71*, 163 (1959).

[16] *H. Spandau* and *A. Beyer*, Naturwissenschaften *46*, 400 (1959).

[17] *F. W. Bennet, H. J. Emeléus*, and *R. N. Haszeldine*, J. chem. Soc. (London) *1953*, 1565.

[18] *W. Kuchen* and *H. Buchwald*, Chem. Ber. *92*, 227 (1959).

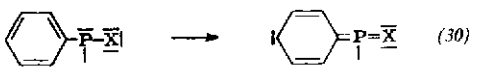
[19] *J. W. B. Reesor* and *G. F. Wright*, J. org. Chemistry *22*, 385 (1957).

[20] *V. N. Kulakova, Yu. M. Zinov'ev*, and *L. Z. Soborovskiy*. Zhur. obshchei Khim. *29*, 3957–9 (1959); Chem. Abstr. *54*, 20846: Synthesis and properties of alkyldifluorophosphines.

[*] Note added in proof: More recently, *W. Kuchen* and *W. Grünewald* have independently prepared tetraphenylcyclotetraphosphane by debromination of $PhPBr_2$ with Mg in an ether/benzene mixture at room temperature. Cf. Angew. Chem. *75*, 576 (1963); Angew. Chem. internat. Edit. *2*, 399 (1963).

However, the condensation proceeded so slowly (after boiling for six hours, only 5 % of the Ph_2PBr had reacted) that this preparation of P_2Ph_4 seemed inexpedient [*].

The decrease in the reactivity of the phosphorus-halogen bond effected by attaching phenyl groups to the phosphorus atom (and by the transition from iodine to fluorine) can perhaps be attributed to the electron-attracting effect of the phenyl groups which causes an electron shift such as



(30)

Thus, the P–X bond becomes less reactive as the number of phenyl groups increases (order of reactivity $PX_3 > PhPX_2 > Ph_2PX$) and as the atomic weight of the halogen decreases (order of reactivity I > Br > Cl > F).

3. Attempts to Prepare a Tetraethylcyclotetraphosphane P_4Et_4

Since no adequate directions for the preparation of ethyldibromophosphane existed at the time of our experiments, ethyldichlorophosphane was used in the dehalogenation with mercury.

$$EtPCl_2 + 2\ Hg \rightarrow 1/n\ (EtP)_n + Hg_2Cl_2 \qquad (31)$$

Very little could be predicted about the prospects of success of this condensation, since replacement of $PhPBr_2$ *(26)* by $EtPCl_2$ *(31)* necessarily produces both an increase in the reactivity of the phosphorus-halogen bond (caused by replacement of the phenyl group by an ethyl group) and a simultaneous decrease (caused by replacement of the bromine atom by a chlorine atom). The experiment showed that the latter effect predominates. No Hg_2Cl_2 separated out even after refluxing a benzene solution of $EtPCl_2$ with excess Hg for 10 hours. The ethyldichlorophosphane was recovered unaltered. Thus, reaction *(31)* did not take place.

In the meantime, *Issleib* and *Mitscherling* [12] obtained tetraethylcyclotetraphosphane in the form of a colorless oil by treating $EtPH_2$ with $EtPCl_2$ in toluene. Examples of other known cyclotetraphosphanes are: tetracyclohexylcyclotetraphosphane (colorless crystals, m.p. 220 °C), which was synthetized by *Issleib* and *Seidel* [21] from $C_6H_{11}PH_2$ and $C_6H_{11}PCl_2$ in boiling toluene, and tetrakis(trifluoromethyl)-cyclotetraphosphane (colorless crystals, m.p. 66.4 °C, b.p. 145 °C), which was obtained by *Burg* and *Mahler* [7] by various methods.

IV. Attempts to Prepare Organo Derivatives of Branched-Chain Polyphosphanes P_4H_6 and P_6H_8 by Condensation of Phosphorus Halides PX_3 and P_2X_4 with Organoalkaliphosphanes $R_2PNa(Li)$

Branched-chain organo-substituted polyphosphanes with four and six phosphorus atoms per molecule were prepared by the condensation of phosphorus halides with organoalkaliphosphanes described in Section II.

The phosphorus halides used were PCl_3 (or PBr_3) and P_2I_4, the organoalkaliphosphanes were Ph_2PNa and Et_2PLi.

1. Hexaphenyltetraphosphane $P(PPh_2)_3$

A solution of phosphorus tribromide in ether was added dropwise to a stirred suspension of excess sodium diphenylphosphane in ether at −40 °C in the absence of air. After removal of the precipitate of NaBr formed by filtration and concentration of the ether solution, an orange oil of high bromine content was obtained, from which no homogeneous compound could be isolated. The same results were obtained when the reaction was carried out in benzene at 0 °C; here, too, the product had a high halogen content, corresponding to incomplete conversion into $P(PPh_2)_3$ according to:

$$PBr_3 + 3\ NaPPh_2 \rightarrow P(PPh_2)_3 + 3\ NaBr \qquad (32)$$

In order to complete the substitution of the Br atoms of the phosphorus tribromide by PPh_2 groups, *i.e.* in order to attain completion of reaction *(32)*, the experiment was repeated in benzene at room temperature. A frozen mixture of excess Ph_2PNa suspended in benzene and a solution of PBr_3 in benzene was slowly melted in the absence of air and then warmed to room temperature with stirring. The color deepened from yellow (Ph_2PNa) to dark-brown, and NaBr separated out. A brown substance was deposited on the walls of the flask, and brown flakes precipitated from the dark, bromine-free filtered benzene solution.

All the halogen from the PBr_3 used was found on the filter as NaBr. In addition, a brown organophosphorus compound, which was insoluble in the ordinary organic solvents, was also present on the filter.

On evaporation *in vacuo*, the filtrate left a solid brown residue with a lack of homogeneity which could be detected even under the microscope. Extraction of this residue with benzene (which does not dissolve the brown constituent) and addition of petroleum ether to the extract gave a yellow substance of highly variable phosphorus content and molecular weight. The molecular weight in benzene was far below that calculated for a tetraphosphane P_4Ph_6 and, as later experiments showed, fell off to that of tetraphenyldiphosphane on purification by repeated crystallization from benzene/petroleum ether mixtures. On heating at 150 °C *in vacuo*, most of the substance sublimed as colorless tetraphenyldiphosphane. The small residue obtained no longer dissolved in the usual organic solvents, and, on the basis of its phosphorus content (23.3 % P), proved to be a higher oligophosphane P_nPh_{n+2} which could be, for example, P_6Ph_8 (calculated: 23.1 % P).

Reactions between sodium diphenylphosphane and phosphorus trichloride in ether and benzene proceeded analogously.

These preliminary experiments sufficed to yield the conclusion that a branched hexaphenyltetraphosphane is unstable and disproportionates analogously to – but considerably more readily than – pentaphenyltriphosphane (Section I.1). The products are tetraphenyldiphosphane, which has a higher content of phenyl

[*] Note added in proof: More recently, *W. Kuchen* and *W. Grünewald* have obtained tetraphenyldiphosphane by smooth debromination of Ph_2PBr with Mg in an ether/benzene mixture. Cf. Angew. Chem. *75*, 576 (1963); Angew. Chem. internat. Edit. *2*, 399 (1963).

[21] *K. Issleib* and *W. Seidel*, Z. anorg. allg. Chem. *303*, 155 (1960).

groups, and higher molecular-weight polyphosphanes with a lower phenyl content.

$$x\ P_4Ph_6 \rightarrow P_nPh_{n+2} + (x-1)\ P_2Ph_4 \quad (n = 2x + 2). \qquad (33)$$

This conclusion was confirmed by experiments in tetrahydrofuran, in which Ph_2PNa is soluble (cf. Section II.1), so that reaction *(32)* could be carried out in a homogeneous phase and with stoichiometric amounts of Ph_2PNa and PX_3.

A solution of Ph_2PNa in tetrahydrofuran was added dropwise to a stirred solution of PCl_3 in tetrahydrofuran (molar ratio $Ph_2PNa:PCl_3 = 3:1$) at room temperature in the absence of air. The onset of reaction was evident from the color change of the red Ph_2PNa solution added. At first, the mixture produced was only slightly yellow and a yellowish precipitate separated out. When the amount of Ph_2PNa added exceeded the molar ratio $Ph_2PNa:PCl_3 = 2:1$, corresponding to the beginning of the formation of $P(PPh_2)_3$ from $PCl(PPh_2)$, the contents of the flask suddenly turned dark-brown and brown flakes settled out on the walls. After addition of the remaining Ph_2PNa solution and stirring for further 3 hours, the product was separated by filtration into a brown residue R and a dark, chlorine-free filtrate F.

The residue R contained the total chlorine from the PCl_3 as NaCl plus a brown organic phosphorus compound which was insoluble in ordinary organic solvents and which had a phosphorus content of 28.7 % (see below).

Concentration of the filtrate F produced a solid brown residue, from which tetraphenyldiphosphane (1 mole per mole of PCl_3 used) sublimed off on heating at 150–200 °C *in vacuo*. The brown residue remaining after the sublimation was insoluble in the ordinary organic solvents and had a phosphorus content of 30.2 %, *i.e.* it had practically the same composition as the organic phosphorus compound remaining in the residue R after removal of the NaCl. The molar balance indicates that both brown residues have the empirical formula "PPh" (calculated 28.6 % P).

Thus, the reaction between PCl_3 and Ph_2PNa can be explained unequivocally as follows: Hexaphenyltetraphosphane $P(PPh_2)_3$ is formed first via the intermediates $PCl_2(PPh_2)$ and $PCl(PPh_2)_2$ and then condenses even at room temperature, or more rapidly on heating, in the following manner:

$$\ldots + \underline{Ph_2P}\text{–}P(PPh_2)\text{–}\boxed{PPh_2 + Ph_2P}\text{–}P(PPh_2)\text{–}\underline{PPh_2} + \ldots \qquad (34)$$

The condensation splits out P_2Ph_4 (*i.e.* "PPh_2") and proceeds via the stage of higher polyphosphanes P_nPh_{n+2} according to Equation *(33)* [22] to $[P(PPh_2)]_x$ (*i.e.* "PPh") where x is very large [23]. The overall process can be described as follows:

$$x\ P(PPh_2)_3 \rightarrow [P(PPh_2)]_x + x\ P_2Ph_4 \qquad (35)$$

In order to learn something about the stability of the intermediates $PCl_2(PPh_2)$ and $PCl(PPh_2)_2$ of reaction *(32)*, the reaction between PCl_3 and Ph_2PNa was also studied using molar ratios of 1:1 and 1:2.

Molar ratio 1:1. A solution of Ph_2PNa in tetrahydrofuran was added dropwise to a stirred solution of PCl_3 in tetrahydrofuran in a molar ratio of 1:1 at room temperature in the absence of air. The red Ph_2PNa solution was completely decolorized and an orange precipitate separated out.

After filtration, the filter contained an orange residue. The latter consisted of NaCl equivalent to the Ph_2PNa added (1 mole per mole of PCl_3 used) and an orange substance which was insoluble in ordinary organic solvents and which, according to the material balance, was elemental phosphorus ($^2/_3$ mole per mole of PCl_3 used).

Evaporation of the filtrate produced a residue of diphenylchlorophosphane (1 mole per mole PCl_3); the tetrahydrofuran separated by distillation contained phosphorus trichloride ($^1/_3$ mole per mole of PCl_3 used).

This clarified the course of the reaction. The initial monosubstitution product, $PCl_2(PPh_2)$, formed according to the equation

$$PCl_3 + NaPPh_2 \rightarrow PCl_2(PPh_2) + NaCl \qquad (36)$$

is unstable and decomposes spontaneously even at room temperature:

$$P_2Ph_2Cl_2 \rightarrow {}^1/_3\ PCl_3 + {}^2/_3\ P + Ph_2PCl\,. \qquad (37)$$

This decomposition appears much less startling when it is assumed that the reaction is analogous to that of the tetraphosphane $P(PPb_2)_3$ in Equation *(34)*. Thus, $PCl_2(PPh_2)$ condenses to $[-P(Cl)-]_x$ with elimination of Ph_2PCl according to the equation:

$$\ldots + \underline{Cl}\text{–}P(Cl)\text{–}\underline{PPh_2} + \underline{Cl}\text{–}P(Cl)\text{–}\underline{PPh_2} + \ldots \qquad (38)$$

The "PCl" then disproportionates, just as other phosphorus(I) compounds do, to give $^1/_3\ PCl_3$ and $^2/_3$ P.

Molar ratio 1:2. When PCl_3 was treated with Ph_2PNa in a molar ratio of 1:2 (a solution of Ph_2PNa in tetrahydrofuran was added dropwise with exclusion of air to a solution of PCl_3 in tetrahydrofuran), an orange precipitate separated out as before, and the red Ph_2PNa solution was decolorized. Evaporation of the mixture *in vacuo* produced a moist, orange residue, which on heating to 250 °C in vacuo yielded a liquid (Ph_2PCl; 0.64 mole per mole of PCl_3 used) and a sublimate (P_2Ph_4; 0.59 mole per mole of PCl_3 used). In addition to the NaCl corresponding to the Ph_2PNa used (2 moles per mole of PCl_3 added), the residue from the distillation contained an orange substance, which was insoluble in ordinary organic solvents. According to the material balance, this had the empirical formula $P_{1.18}Ph_{0.36}Cl_{0.36}$ and was therefore a phosphorus that still contained phenyl groups and chlorine atoms. Consequently, the initial disubstitution product $PCl(PPh_2)_2$ expected from the equation

$$PCl_3 + 2\ NaPPh_2 \rightarrow PCl(PPh_2)_2 + 2\ NaCl \qquad (39)$$

decomposed according to the empirical equation

$$P_3Ph_4Cl \rightarrow P_{1.18}Ph_{0.36}Cl_{0.36} + 0.64\ Ph_2PCl + 0.59\ P_2Ph_4 \qquad (40)$$

Again, this decomposition seems less peculiar if it is assumed that $PCl(PPh_2)_2$ reacts analogously to $P(PPh_2)_3$ in *(34)* and $PCl_2(PPh_2)$ in *(38)*. Thus, $PCl(PPh_2)_2$ condenses to $[-P(Cl)-P(PPh_2)-]_x$ ("$P_{1.5}PhCl_{0.5}$"):

$$\ldots + \underline{Ph_2P}\text{–}P(Cl)\text{–}\underline{PPh_2} + \underline{Cl}\text{–}P(PPh_2)\text{–}\underline{PPh_2} + \ldots \qquad (41)$$

with elimination of 0.5 PPh_2Cl and 0.5 P_2Ph_4. The condensation product may give up even more Ph_2PCl and $(Ph_2P)_2$, depending on the experimental conditions.

Ph_2PNa also reacts with phosphorus oxychloride and with phosphorus thiochloride (molar ratios 3:1) in tetrahydrofuran. The reaction is similar to that with phosphorus trichloride in that tetraphosphanes $PO(PPh_2)_3$ or $PS(PPh_2)_3$ are not formed. Instead, the reaction yields decomposition products, among which tetraphenyldiphosphane can again be detected. Hence, the decomposition of these tetraphosphanes is probably analogous to that of $P(PPh_2)_3$ in *(35)*.

[22] First condensation stage: P_6Ph_8, corresponding to x = 2 in *(33)*.

[23] The fact that $[P(PPh_2)]_x$ is able to lose a little more P_2Ph_4 is evident from the finding that the amount of P_2Ph_4 obtained was somewhat greater than 1 mole per mole of P_4Ph_6 (found 1.05 mole), and that the high polymeric residue contained somewhat more phosphorous than corresponds to the composition $[P(PPh_2)]_x$ (found 30.2, instead of 28.6% P).

2. Hexaethyltetraphosphane $P(PEt_2)_3$

The hexaethyl analogue of branched-chain hexaphenyltetraphosphane is, as might be expected, even less stable than the latter. It is formed analogously to *(32)* by the reaction of PCl_3 with 3 moles of $LiPEt_2$ in ether in the absence of air at −10 °C. It polymerizes by analogy to Equation *(34)* with elimination of P_2Et_4 via

$$\ldots + Et_2P\text{–}P(PEt_2)\text{–}PEt_2 + Et_2P\text{–}P(PEt_2)\text{–}PEt_2 + \ldots \quad (42)$$

the expected intermediate product $[-P(PEt_2)-P(PEt_2)-]_x$ which keeps on condensing, with further elimination of P_2Et_4 [24], until a product rich in phosphorus (an orange substance) is formed. Instead of an equation similar to Equation *(35)*, the following modified condensation equation results for the process [25]:

$$x\ P(PEt_2)_3 \rightarrow [P(PEt_2)_{1-a}]_x + x\,(1 + a/2)\ P_2Et_4 \quad (43)$$

When a = 1 (complete elimination of all the Et groups as P_2Et_4), this equation becomes

$$x\ P(PEt_2)_3 \rightarrow [P]_x + 1.5\ x\ P_2Et_4 \quad (44)$$

3. Octaphenylhexaphosphane $P_2(PPh_2)_4$

Octaphenylhexaphosphane was formed by treating sodium diphenylphosphane with tetraiododiphosphane in benzene for three days at room temperature in the absence of air.

$$P_2I_4 + 4\ NaPPh_2 \rightarrow P_2(PPh_2)_4 + 4\ NaI \quad (45)$$

Again, as might have been expected, the octaphenylhexaphosphane could not be obtained as such, but only in the form of its decomposition products. Evaporation of the dark filtrate yielded a brown solid with a molecular weight which was far below that calculated for P_6Ph_8 and from which colorless P_2Ph_4 sublimed off on heating to 150 °C *in vacuo*. The decomposition is probably analogous to that of P_4Ph_6 in *(34)*,

$$\ldots + Ph_2P\text{–}P(PPh_2)\text{–}P(PPh_2)\text{–}PPh_2 + Ph_2P\text{–}P(PPh_2)\text{–}P(PPh_2)\text{–}PPh_2 + \ldots \quad (46)$$

the products being $[-P(PPh_2)-P(PPh_2)-]_x$ (*i.e.* "PPh") and P_2Ph_4 (*i.e.* "PPh_2").

In summary, it can therefore be stated that branched polyphosphanes of the type P_nR_{n+2} ($n \geq 4$), in which the phosphorus has an average oxidation number of $(n + 2)/n$, are very unstable and disproportionate spontaneously to phosphanes with oxidation numbers for the phosphorus of +1 ("PR") and +2 ("PR_2").

$$P_nR_{n+2} \rightarrow (n-2)\ "PR" + 2\ "PR_2". \quad (47)$$

[24] The orange residue remaining after the solvent had been removed was heated to 150 °C *in vacuo* in order to isolate the P_2Et_4.

[25] In the example studied by us was a = 0.25, which means that three-quarters of the Et groups introduced as Et_2PNa were incorporated into the P_2Et_4 and one-quarter into the orange solid. In the case of the phenyl compound P_4Ph_6, for which, according to *(35)*, a 0, the corresponding figures were two-thirds and one-third.

The former can disproportionate further, although less readily, to elemental and divalent phosphorus.

$$2\ "PR" \rightarrow "P" + "PR_2" \quad (48)$$

On the other hand, the straight-chain polyphosphanes P_nR_{n+2} are markedly more stable.

V. Preparation of Phenyl Derivatives of a Decaphosphane $P_{10}H_6$ (an Adamantane Analogue) and its Oxide $P_{10}H_6O_4$ by Condensation of Phosphorus Trichloride or Phosphorus Oxychloride with Phenyldilithiumphosphane

The preparation of polyphosphanes P_nR_{n+2} (where R = alkyl or aryl) by condensation of di- and trifunctional phosphorus halides (RPX_2, PX_3, P_2X_4) with monofunctional organoalkaliphosphanes (R_2PNa, R_2PLi) was described in Sections II and IV.

$$RPX_2 + 2\ MPR_2 \rightarrow RP(PR_2)_2 + 2\ MX \quad (49)$$

$$PX_3 + 3\ MPR_2 \rightarrow P(PR_2)_3 + 3\ MX \quad (50)$$

$$P_2X_4 + 4\ MPR_2 \rightarrow P_2(PR_2)_4 + 4\ MX \quad (51)$$

(X = Cl, Br, I; M = Li, Na)

In this section, the condensation of trifunctional phosphorus halides PX_3 with difunctional organoalkaliphosphanes RPM_2 will be described. This reaction was expected to involve possible formation of decaphosphanes $P_4(PR)_6$ with structures of the adamantane type.

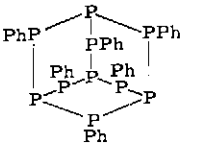
$$4\ PX_3 + 6\ M_2PR \rightarrow P_4(PR)_6 + 12\ MX \quad (52)$$

1. Hexaphenyldecaphosphane $P_4(PPh)_6$

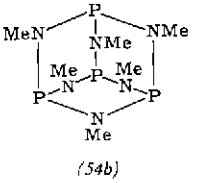
A solution of phosphorus trichloride in ether was added dropwise to a stirred yellow suspension in ether of phenyldilithiumphosphane [9] (molar ratio PCl_3:$PhLi_2$ = 2:3) with exclusion of air at −80 °C. A vigorous reaction

$$4\ PCl_3 + 6\ Li_2PPh \rightarrow P_4(PPh)_6 + 12\ LiCl \quad (53)$$

occurred immediately, accompanied by precipitation. The contents of the flask became in turn orange, then red and finally, on addition of further PCl_3, yellow. The mixture was heated to room temperature, filtered, and the filtrate evaporated *in vacuo*; however, only a small residue was obtained, most of the product remained on the filter. The lithium chloride was washed out with water leaving a yellow halogen-free solid. Analysis and a molecular-weight determination in benzene, gave a composition and molecular weight for the latter cor-



(54a)



(54b)

responding to $P_{10}Ph_6$ (found 40.1% P; calculated 40.1% P; molecular weight: found 775; calculated 772). In accordance with its production from PCl_3 and $PhPLi_2$ it must have a structure *(54a)* analogous to adamantane; this structure was also recently found in a homologous nitrogen compound $P_4(NMe)_6$ *(54b)*, obtained from phosphorus trichloride and methylamine [26].

Accordingly, the adamantane-type skeleton of $P_{10}Ph_6$ is formed from phosphorus atoms by condensation of four P_6 rings to give a polycyclic system. Branched $P(P\langle)_3$ groupings are evidently possible in this form although they are unstable outside of such a ring system (see Section IV). The Stuart model of the compound $P_4(PPh)_6$ shows that an adamantane-type structure is possible and that, in addition, the adamantane-type skeleton provides sufficient room for steric requirements of the phenyl groups.

The $P_{10}Ph_6$ may also be separated from LiCl by extraction with benzene instead of by washing out the LiCl with water.

$P_4(PPh)_6$ is very soluble in benzene, toluene, xylene, chloroform, dioxane, tetrahydrofuran, methylene chloride, and trichloroethylene, slightly soluble in ether, and insoluble in n-hexane, petroleum ether, methanol, and water. Its stability towards oxygen is remarkable: the compound is not altered even on prolonged standing in air (provided moisture is excluded). It begins to soften above 60 °C. After prolonged heating at 100–120 °C, it is still completely soluble in benzene, but has a higher molecular weight (889) than before (775). Following extended heating at 200–210 °C, it no longer dissolves completely in benzene. The simplest explanation for this is the assumption of formation of higher polymers $[P_2(PPh)_3]_n$, where $n > 2$, analogous to the behavior of arsenic trioxide As_2O_3, which occurs not only in dimeric, but also in higher polymeric forms $[As_2O_3]_n$. Because of this tendency to polymerize, sublimation of the compound *in vacuo* is not possible.

X-Ray diffraction patterns show that the direct product from reaction *(53)* is at first roentgenographically amorphous. However, after dissolution in benzene and slow reprecipitation with petroleum ether, lines appear in the patterns which indicate crystalline regions. The infrared spectrum contains aromatic C–H vibration peaks at 3.3 μ and 13.6 μ, a C–H vibration peak characteristic for the phenyl radical at 14.5 μ, and a peak for the P–Ph vibration just below 7 μ.

Hexaphenyldecaphosphane reacts with excess methyl iodide in benzene with cleavage of the P–P bonds and precipitation of iodine.

[26] *R. R. Holmes* and *J. A. Forstner*, J. Amer. chem. Soc. *82*, 5509 (1960).

2. Hexaphenyldecaphosphane Tetroxide $P_4O_4(PPh)_6$

The surprising stability of hexaphenyldecaphosphane to oxygen raised the question whether phosphorus oxychloride could not replace PCl_3 in the reaction with phenyldilithiumphosphane and thus produce the oxide $P_4O_4(PPh)_6$.

$$4\ POCl_3 + 6\ Li_2PPh \rightarrow P_4O_4(PPh)_6 + 12\ LiCl \qquad (55)$$

In $P_4O_4(PPh)_6$, an oxygen atom is attached to each of the four non-phenylated phosphorus atoms of the adamantane type skeleton *(54a)*. As it turns out, this reaction is indeed possible.

A solution of $POCl_3$ in ether was added dropwise at −80 °C to a yellow suspension of $PhPLi_2$ in ether. A vigorous reaction took place and the contents of the flask turned first orange, then red, and finally yellow. The residue obtained on evaporation of the ether was extracted with benzene and the extract yielded a yellow solid, corresponding in composition and molecular weight to the formula $P_4O_4(PPh)_6$ (found 36.7% P, calculated 36.9% P; molecular weight: found 831, calculated 836).

Like the oxygen-free compound, $P_4O_4(PPh)_6$ is very soluble in benzene, toluene, tetrahydrofuran, dioxane, and chloroform, slightly soluble in ether, and insoluble in n-hexane. On standing in air, it deliquesces within a day. It begins to soften above 60 °C. After heating to 200 °C, it no longer dissolves completely in benzene; this may probably be explained by the formation of polymers $[(PO)_2(PPh)_3]_n$ ($n > 2$). The infrared spectrum of $P_4O_4(PPh)_6$ agrees with that of $P_4(PPh)_6$, with the difference that an additional P–O band is observed at 8 μ.

Summary

In summary, it can be stated that phosphorus is able to form higher-membered chain and ring molecules just like its two neighbors in the periodic table, silicon and sulfur. Further investigation in this field therefore promises a rich harvest of observations and will certainly contribute not only to the closing of existing gaps in chemical systematics, but also to an expansion of our knowledge of the bonding behavior and reactivity of phosphorus. In particular, the studies carried out so far with organo-substituted polyphosphanes P_nR_{n+2} justify the hope that in addition to the parent substance P_2H_4 (the only polyphosphane known up to now) higher straight-chain polyphosphanes P_nH_{n+2}, such as P_3H_5 and P_4H_6, will be isolable at lower temperatures. Very promising indications of this are already to be found in the literature [27].

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German version: Angew. Chem. *75*, 814 (1963)

[27] *M. Baudler* and *L. Schmidt*, Naturwissenschaften *46*, 577 (1959).

Syntheses of *s*-Triazine and Substituted *s*-Triazines

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Dedicated to Prof. Dr. Karl Winnacker on the occasion of his 60th birthday

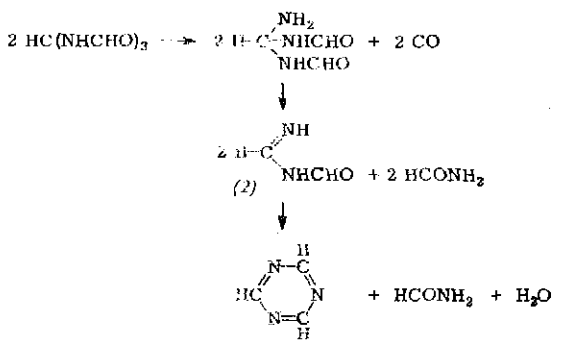
In the last account of our investigations in the amide field [1], *we reported inter alia on the preparation and reactions of trisformamidomethane. Further work with this compound led to simple syntheses particularly of heterocyclic compounds. Following the pattern of these syntheses, compounds other than trisformamidomethane were employed for formylation and ring-closure; these included formates, orthoformates, formamidine, dimethylformamide diethylacetal, and formamide. Part of this recent research is reported below.*

I. Introduction

On heating trisformamidomethane above its melting point (165–166 °C) *s*-triazine is obtained. To clarify this formation of triazine we investigated the decomposition of trisformamidomethane *(1)* [2]. Practically complete recovery of *s*-triazine, formamide, and carbon monoxide as decomposition products suggested the following equation:

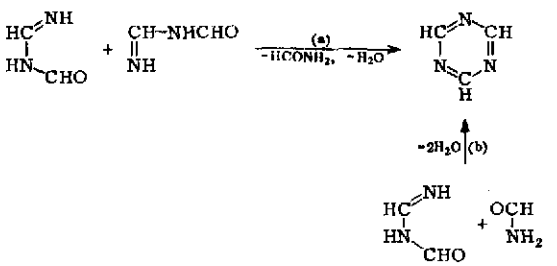
$$\underset{(1)}{2\ HC(NHCHO)_3} \rightarrow \underset{s\text{-Triazine}}{(HCN)_3} + 3\ HCONH_2 + 2\ CO + H_2O$$

From this equation, the following sequence of reactions can be deduced:



$$2\ HC(NHCHO)_3 \rightarrow (HCN)_3 + 3\ HCONH_2 + 2\ CO + H_2O$$

In this scheme, the crucial intermediate for the formation of *s*-triazine is formylformamidine *(2)*, on which we had previously based the explanation of our reactions [1]. The formation of triazine may be explained either by condensation of two molecules of formylformamidine with loss of formamide and water (a) or by condensation of formylformamidine and formamide with loss of water (b):



We prefer the condensation mechanism (a) on the basis of the following experiments:

1. On performing the decomposition in formamide, (b) should lead to a higher yield of triazine than without formamide. However, in fact the yield is not altered.

2. Formylguanidine can be converted by self-condensation (140 °C) into 2,4-diamino-*s*-triazine [3]. The same compound was obtained by *Grundmann* et al. [4] from formylguanidine by heating it in the presence of formamide to 190–220 °C. Had formamide taken part in the reaction according to (b), then monoamino-*s*-triazine would have been formed.

II. Syntheses of Substituted *s*-Triazines

The experiments and theoretical considerations carried out in connection with the formation of *s*-triazine indicated *inter alia* the following possibilities for preparing substituted triazines (substituted especially in the 2- and 4-positions):

1. Self-condensation of an *N*-formyl compound of the type HN=C–NHCHO.

X

[1] *H. Bredereck, R. Gompper, H. G. v. Schuh,* and *G. Theilig,* Angew. Chem. *71*, 753 (1959).

[2] *H. Bredereck, F. Effenberger,* and *A. Hofmann,* Chem. Ber., in the press; *A. Hofmann,* Diploma Thesis, Technische Hochschule Stuttgart, 1961.

[3] *K. Sugino* and *M. Yamashita,* Jap. Pat. 5284 (1952); Chem. Abstr. *48*, 9412 (1954).

[4] *C. Grundmann, L. Schwennicke,* and *E. Beyer,* Chem. Ber. *87*, 19 (1954).

2. The action of a formylating agent on compounds of the type $HN=\underset{\displaystyle X}{\overset{|}{C}}-NH_2$ and immediate self-condensation.

Of these two possibilities, the second reaction was to be preferred from the outset.

1. Self-condensation

We have already mentioned that *Sugino* and *Yamashita* [3] and *Grundmann* et al. [4] obtained 2,4-diamino-*s*-triazine from formylguanidine. The self-condensation of *N*-formylurea (X=OH) led to only a small yield (13 %) of 2,4-dihydroxy-*s*-triazine (see below). On heating equal parts of *N*-formylurea and formylguanidine ($X=NH_2$), a good yield (61 %) of 2-amino-4-hydroxy-*s*-triazine was obtained (see below). It is noteworthy that of the three compounds that are theoretically possible here, *viz.* 2,4-dihydroxy-, 2,4-diamino-, and 2-amino-4-hydroxy-*s*-triazine, only the latter is formed.

The interaction of formylguanidine and trisformamidomethane is to be regarded as a reaction between different *N*-formyl compounds [5]. The formylformamidine initially formed from the trisformamidomethane reacts with formylguanidine to give amino-*s*-triazine (yield: 82 %).

2. Formylation and Self-condensation

a) *Mono- and Diamino-s-triazines*

In our previous account [1], we already reported the conversion of guanidine into mono- or diamino-*s*-triazine with trisformamidomethane or formamide. In our later experiments, formylation and ring closure were also accomplished by the use of formic acid, formates and orthoformates, and dimethylformamide diethylacetal, $(H_3C)_2N-CH(OC_2H_5)_2$. The last-named compound has become readily accessible from the dimethylformamide/dimethyl sulfate complex and sodium ethoxide in alcoholic solution [6]. Whereas the preparation of diamino-*s*-triazine from guanidine and formamide required temperatures of 120 and 140 °C (yield 36 % and 44 %, respectively) [7], the reaction with dimethylformamide diethylacetal required a temperature of only 70–80 °C and gave a yield of 92 %. The reaction mechanism is discussed below.

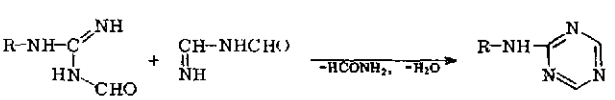
In this connection, our previously reported preparation of diamino-*s*-triazine in 73 % yield from dicyandiamide and formamide should also be mentioned [7, 8].

Following the experiments with free guanidine, it was logical that substituted guanidines should be tried. Dependent on the co-reactant, *N*-substituted mono- or diamino-*s*-triazines were to be expected. The reactions of substituted guanidines with trisformamidomethane in dimethylformamide as solvent led to substituted monoamino-*s*-triazines [7]. These experiments were done a few years ago but were completed by some further examples in the past year (Table 1).

Table 1. Summary of monoamino-*s*-triazines from trisformamidomethane and guanidine derivatives.

Guanidine	*s*-Triazine	Yield [%]
Guanidine	2-Amino-	83
N-Methyl-	2-Methylamino-	63
N-Ethyl-	2-Ethylamino-	41
N-n-Propyl-	2-n-Propylamino-	42
N-Isopropyl-	2-Isopropylamino-	39
N-n-Butyl-	2-n-Butylamino-	58
N-Phenyl-	2-Anilino-	99
N-Benzyl-	2-Benzylamino-	62
N-*p*-Tolyl-	2-*p*-Toluidino-	60
N,*N*-Dimethyl-	2-Dimethylamino-	64
N,*N*-Pentamethylene-	2-Piperidino-	75
1,4-Diguanidino-benzene	1,4-Bis-*s*-triazinyl-amino-benzene	75
p-Methoxyphenyl-	2-*p*-Anisidino-	95
Formyl-	2-Amino-	82
Sulfa-	2-*p*-Formylamino-benzenesulfonamido-	23

The formation of the *N*-substituted amino-*s*-triazines may be explained in three ways: as a reaction between the guanidine and formylformamidine (formed from trisformamidomethane), or between the formylguanidine and formamidine, or finally between the formylguanidine and formylformamidine. The formylguanidine can be formed here from formylformamidine or formamide and the guanidine. Formamide is liberated by the decomposition of trisformamidomethane (see above).



If the substituted guanidines are treated with formates or dimethylformamide diethylacetal, *N*-mono- or *N*,*N*'-disubstituted 2,4-diamino-*s*-triazines are obtained (Table 2).

There are several methods of making *N*-monosubstituted diamino-*s*-triazines, *e.g.* via the reaction of biguanidines with formylating agents such as ethyl formate [9], by the reaction of 4-amino-2-methylthio-*s*-triazine with amines [7], or by reduction of 2-amino-4-butylamino-6-chloro-*s*-triazine [10]. Our new synthesis is simpler than these previous ones.

Of the *N*-disubstituted diamino-*s*-triazines, only the 2,4-dianilino-*s*-triazine (prepared in several stages) was known before [11–13].

---

[5] *A. Hofmann*, Ph. D. Thesis, Technische Hochschule Stuttgart, 1963.

[6] *H. Bredereck, F. Effenberger*, and *G. Simchen*, Angew. Chem. *73*, 493 (1961); Chem. Ber. *96*, 1350 (1963).

[7] *H. Bredereck, O. Smerz*, and *R. Gompper*, Chem. Ber. *94*, 1883 (1961).

[8] *O. Smerz*, Diploma Thesis, Technische Hochschule Stuttgart, 1958.

[9] *C. G. Overberger* and *S. L. Shapiro*, J. Amer. chem. Soc. *76*, 93 (1954).

[10] *F. C. Schaefer, I. Hechenbleikner, G. A. Peters*, and *V. P. Wystrach*, J. Amer. chem. Soc. *81*, 1466 (1959).

[11] *C. Grundmann* and *A. Kreutzberger*, J. Amer. chem. Soc. *77*, 44 (1955).

[12] *J. T. Thurston, J. R. Dudley, D. W. Kaiser, I. Hechenbleikner, F. C. Schaefer*, and *D. Holm-Hansen*, J. Amer. chem. Soc. *73*, 2981 (1951).

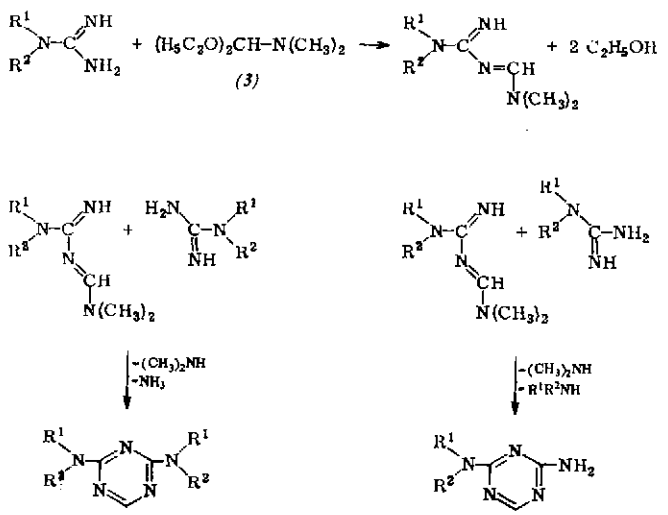
[13] *I. Hechenbleikner*, J. Amer. chem. Soc. *76*, 3032 (1954).

Table 2. *N*-Mono- and *N,N'*-disubstituted 2,4-diamino-*s*-triazines.

Guanidine	Formylating Agent	*s*-Triazine	Yield [%]	M.p. [°C]
Guanidine	Dimethylformamide diethylacetal	2,4-Diamino-	92	323
Methyl-		2-Amino-4-methylamino-	33	239–240
Ethyl-		2-Amino-4-ethylamino-	63	198
N,N-Pentamethylene-		2-Amino-4-piperidino-	66	195
N-Methyl-*N*-phenyl-		2-Amino-4-(*N*-methylanilino)-	15	186
Cyclohexyl-		2-Amino-4-cyclohexylamino-	50	162
		+ 2,4-Bis(cyclohexylamino)-	15	262–263
Isopropyl-	Ethyl formate	2,4-Bis(isopropylamino)-	27	213
n-Butyl-		2,4-Bis-(n-butylamino)-	18	149
Phenyl-	Dimethylformamide diethylacetal	2,4-Dianilino-	54	315
m-Tolyl-		2,4-Bis-(*m*-tolylamino)-	31	244
p-Tolyl-		2,4-Bis-(*p*-tolylamino)-	48	323
Benzyl-		2,4-Bisbenzylamino-	43	226–227
p-Methoxyphenyl-		2,4-Bis-(*p*-anisidino)-	33	309

All the monosubstituted 2,4-diamino-*s*-triazines investigated so far have diuretic properties.

Scheme 1 demonstrates the formation of *N*-mono- and *N,N'*-disubstituted diamino-*s*-triazines using dimethylformamide diethylacetal *(3)*.



Scheme 1. Formation of *N*-mono- and *N,N'*-disubstituted diamino-*s*-triazines from guanidines and dimethylformamide diethylacetal.

It should be mentioned that primary elimination of ammonia or of RR'NH with formation of the biguanidine can also be assumed. The latter is then converted into the diamino-*s*-triazine by reaction with dimethylformamide diethylacetal and elimination of dimethylamine. In the experiments carried out with ethyl formate, formylation occured instead of the introduction of the dimethylaminomethylene group, followed by loss of water instead of elimination of dimethylamine.

It cannot yet be predicted from the work done so far whether formation of the *N*-mono- or *N,N'*-disubstituted diamino-*s*-triazines will occur. Steric influences certainly play no part.

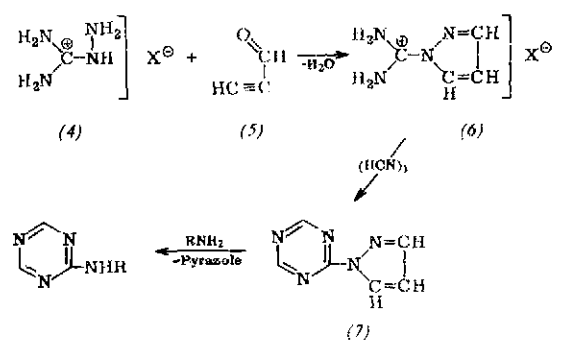
The fact that not every formylating agent is equally well suited to the synthesis of diamino-*s*-triazines is indicated by the instance of formic acid. With phenylguanidine, this first forms the formate; however, prolonged heating at 165 °C (the decomposition temperature of the formate) also gives rise to 2,4-dianilino-*s*-triazine.

We found another simple route to *N*-substituted monoamino-*s*-triazines by synthetizing 2-(pyrazol-1-yl)-*s*-triazine *(7)* and treating it with amines (Table 3). On

Table 3. Summary of the *N*-substituted monoamino-*s*-triazines obtained from 2-(pyrazol-1-yl)-*s*-triazine and amines.

Amine	*s*-Triazine	Yield [%]	M.p. [°C]
Ammonia	2-Amino-	92	224–225
Hydrazine	2-Hydrazino-	74	178–179
Methyl-	2-Methylamino-	79	109–110
Dimethyl-	2-Dimethylamino-	49	85–88
Ethyl-	2-Ethylamino-	76	64–66
Butyl-	2-Butylamino-	59	61–62
Benzyl-	2-Benzylamino-	63	105–106
Cyclohexyl-	2-Cyclohexylamino-	52	133–134
Morpholine	2-Morpholino-	72	106–108
Aniline	2-Anilino-	19	170–172
p-Toluidine	2-(*p*-Toluidino)-	59	210–212
p-Nitroaniline	2-(*p*-Nitroanilino)-	54	302–305

reaction of aminoguanidine *(4)* (as its bicarbonate) with propargylaldehyde *(5)* in the presence of hydrochloric acid in the cold, 1-amidinopyrazole *(6)* was obtained as its hydrochloride in 93 % yield, and was readily converted into the free compound with ammonia in 89 % yield. For the synthesis of the 2-(pyrazol-1-yl)-*s*-triazine *(7)*, the hydrochloride was treated with triazine in methanolic solution at room temperature (yield: 87 %).



2-Anilino-*s*-triazine is obtained only with a large excess of aniline, otherwise *N,N',N''*-triphenylguanidine is formed. Cleavage may be accomplished by nucleophilic agents in general instead of with ammonia or amines.

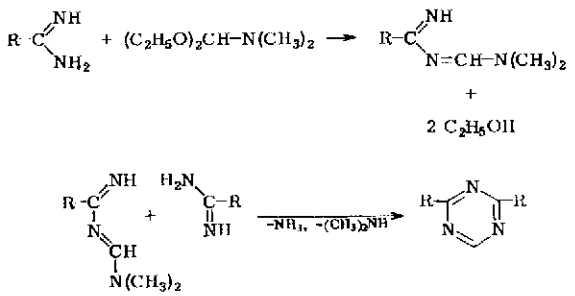
b) *Mono- and Disubstituted s-Triazines*

Formylbenzamidine is the only formylamidine recorded in the literature [4]. However, on repeating the work, we established that the compound is in fact 2,4-diphenyl-*s*-triazine. Our attempts to prepare a formylamidine were all of no avail. Benzamidine, for example, gave diphenyl-*s*-triazine with ethyl formate even at 30 °C. This finding led us to a simple synthesis of di- and monosubstituted *s*-triazines: reaction of amidines with ethyl formate or dimethylformamide diethylacetal gave 2,4-disubstituted *s*-triazines (Table 4).

Table 4. 2,4-Disubstituted *s*-triazines synthetized from amidines and formylating agents.

Amidine	Formylating Agent	*s*-Triazine	Yield [%]	M.p. [°C]	B.p. [°C/735 mm]
Acet-	Ethyl formate	2,4-Dimethyl-	39	45—46	142
Propion-	Ethyl formate	2,4-Diethyl-	35	—	172
Benz-	Dimethylformamide diethylacetal	2,4-Diphenyl-	37	85—87	—
Phenylacet-	Dimethylformamide diethylacetal	2,4-Dibenzyl-	13	80—82	—
Nicotinic	Ethyl formate	2,4-Dipyrid-3-yl-	11	199—202	—

The course of the reaction is shown in Scheme 2.



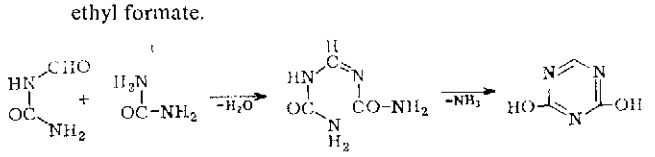
Scheme 2. Formation of 2,4-disubstituted *s*-triazines from amidines and dimethylformamide diethylacetal.

c) *2,4-Dihydroxy-, 2-Amino-4-hydroxy-, and 2-Amino-4-methylthio-s-triazine*

The principle of treating a guanidine or amidine with a formylating agent was extended to urea and thiourea. The experiments described in this section have not yet been concluded.

Heating urea with triethyl orthoformate at 165 °C led to *N,N'*-dicarbamoylformamidine *(8)*, which was converted by longer heating at 175 °C into 2,4-dihydroxy-*s*-triazine *(9)* with elimination of ammonia.

Around the same time, *Piskala* and *Gut* [14] synthetized 2,4-dihydroxy-*s*-triazine, from *N,N'*-dicarbamoylformamidine by condensation with sodium alkoxide, and from biuret and ethyl formate.



(8) *(9)*

[14] *A. Piskala* and *J. Gut*, Collect. Czechoslov. Chem. Commun. *26*, 2519 (1961).

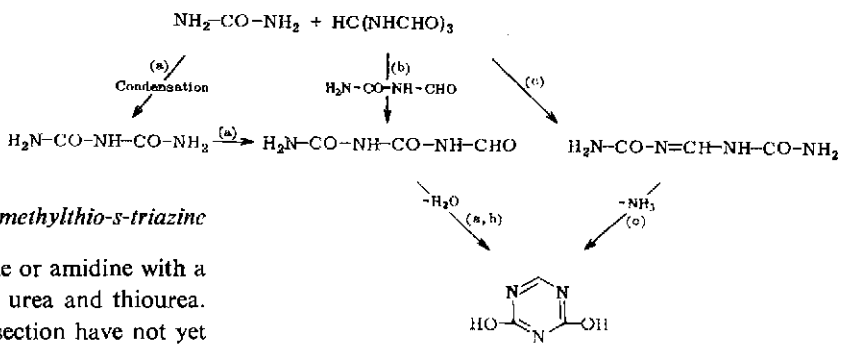
Reaction of urea with trisformamidomethane led directly to dihydroxy-*s*-triazine in 43 % yield. This result was surprising in comparison with the reaction with monoamino-*s*-triazines (see above). By analogy, the formation of monohydroxy-*s*-triazine was to be expected. There are again various courses of reaction conceivable for the formation of dihydroxy-*s*-triazine from urea and trisformamidomethane:

(a) Condensation of urea to biuret, formylation of biuret to formylbiuret, and ring closure with elimination of water.

(b) Reaction of urea with trisformamidomethane to formylurea, followed by condensation to formylbiuret with elimination of formamide, and ring-closure with elimination of water.

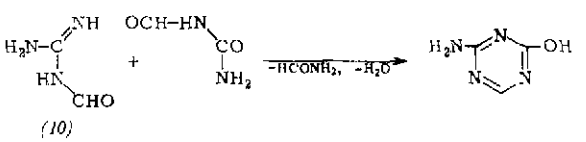
(c) Reaction of urea with trisformamidomethane – corresponding to the reaction of amines with trisformamidomethane giving amidines (see below) – to give *N,N'*-dicarbamoylformamidine, the ring closing with elimination of ammonia.

Following the direct synthesis of dihydroxy-*s*-triazine, we also attempted to prepare 4-amino-2-hydroxy-*s*-triazine directly from urea, guanidine, and a formylating



agent. The use of ethyl orthoformate or formamide led to the required triazine in 40 % yield.

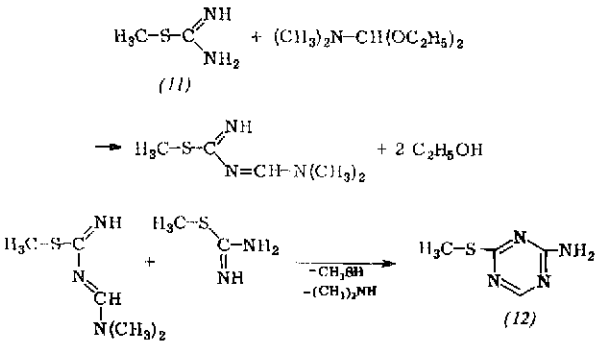
There are several possible explanations for the course of the reaction. In the following, we formulate the conversion as a reaction between initially formed formylguanidine *(10)* and formylurea:



(10)

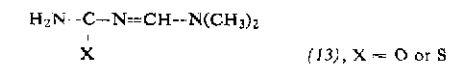
In previous work [7], we had already used *S*-methylisothiourea *(11)* and formamide to obtain 2-methylthio-4-amino-*s*-triazine *(12)*. We now prepared the same com-

pound in 56 % yield using dimethylformamide diethylacetal in place of formamide.



(11)

The reaction with formamide may be formulated similarly as proceeding through *N*-formyl-*S*-methylisothiourea. If loss of ammonia occurs in place of the elimination of methylthiol, a dimethylthio-*s*-triazine should be formed. This compound can in fact be isolated from the reaction with formamide in about 9 % yield. Surprisingly, the reactions of dimethylformamide diethylacetal with urea and thiourea did not lead to *s*-triazines; instead, the reaction remains at the stage of the dimethylaminomethylene compounds *(13)*. These are so stable that they do not form 2,4-disubstituted *s*-triazines even when they are heated until they decompose.



(13), X = O or S

III. Syntheses of Substituted *N,N*-Dimethylamidines

Since the dimethylaminomethylene compounds may be converted by elimination of dimethylamine into *N*-formyl compounds [15], they may be regarded as potential *N*-formyl compounds. Dimethylformamide diethylacetal can accordingly be regarded as a "formylating agent".

Alternatively, the dimethylaminomethylene compounds can be regarded as formamidines because of their –N=CH–N= grouping. *N,N*-Dimethylamidines of this type were to be expected in general from the reaction of dimethylformamide diethylacetal with primary amines.

N,N-Dimethyl-*N'*-*p*-tolylformamidine has been synthetized by *H. Meerwein* et al. [15a] from dimethylformamide diethylacetal and *p*-toluidine.

The compounds were in fact obtained in good to very good yields by warming in a little alcohol (Table 5).

It is noteworthy that of the compounds tested sulfaguanidine does not yield an *s*-triazine but only forms the bis-dimethylaminomethylene compound. It is also interesting that picramide, which is not formylated by any of the usual formylating agents, yields an "*N*-formyl" compound. The new method is much simpler in comparison to the amidine synthesis from the dimethylformamide/phosphorus oxychloride complex and amines reported previously by us [16].

It should be mentioned that we were also able to make other formamidines from trisformamidomethane and amines (Table 6) [17]. These compounds were known previously and had been made from the amines with formylating agents such as ethyl orthoformate, ethyl formate, formic acid, formamide, *etc.*

Table 5. Substituted *N,N*-dimethylamidines made from amines and dimethylformamide diethylacetal.

Amine	Amidine	Yield [%]	B.p. [°C/mm]	M.p. [°C]
2-Aminopyridine	*N,N*-Dimethyl-*N'*-pyrid-2-ylformamidine	91	67/0.02	34–36
3-Aminopyridine	*N,N*-Dimethyl-*N'*-pyrid-3-ylformamidine	64	80/0.1	–
4-Aminopyridine	*N,N*-Dimethyl-*N'*-pyrid-4-ylformamidine	91	92/0.05	54–60
3-Amino-1,2,4-triazole	*N,N*-Dimethyl-*N'*-(1,2,4-triazol-3-yl)formamidine	87		165
4-Amino-1,2,4-triazole	*N,N*-Dimethyl-N'-(1,2,4-triazol-4-yl)formamidine	83		129
p-Nitroaniline	*N,N*-Dimethyl-*N'*-(*p*-nitrophenyl)formamidine	91		86
m-Nitroaniline	*N,N*-Dimethyl-*N'*-(*m*-nitrophenyl)formamidine	78	195/10	–
o-Nitroaniline	*N,N*-Dimethyl-*N'*-(*o*-nitrophenyl)formamidine	89	189/10	
Picramide	*N,N*-Dimethyl-*N'*-(2,4,6-trinitrophenyl)formamidine	95		182
5-Amino-1,2,3,4-tetrazole	*N,N*-Dimethyl-*N'*-(1,2,3,4-tetrazol-5-yl)formamidine	81		200
Sulfaguanidine	ω,ω'-Bis-(*N,N*-dimethylformamidino)sulfaguanidine	87		184–186
2,4-Diamino-*s*-triazine	2,4-Bis-(*N,N*-dimethyl-formamidino)-*s*-triazine	88	–	235–237

Table 6. Formamidines made from amines and trisformamidomethane.

Amine	Amidine	Yield [%]
β-Naphthylamine	*N,N'*-Di-β-naphthylformamidine	40
4-Aminobiphenyl	*N,N'*-Di-4-biphenylylformamidine	43
3-Amino-*s*-triazole	*N*-(*s*-Triazol-3-yl)formamidine	13
o-Phenylenediamine	Benzimidazole	71

N-Monosubstituted formamide derivatives were formed as by-products. We obtained the *N*-(*s*-triazol-3-yl)-formamidine only on heating the *N*-(*s*-triazol-3-yl)-formamide formed first above its melting point. From the reactions with benzylamine and ethylenediamine we were able to isolate only the corresponding formamide derivatives *N*-benzylformamide and *N,N'*-bisformamidoethane and not the anticipated amidines *N,N'*-dibenzylformamidine and Δ²-imidazoline, which like benzimidazole can be regarded as a cyclic formamidine.

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German version: Angew. Chem. 75, 825 (1963)

[15] *H. Eilingsfeld, M. Seefelder*, and *H. Weidinger*, Angew. Chem. 72, 836 (1960).

[15a] *H. Meerwein, W. Florian, N. Schön*, and *G. Stopp*, Liebigs Ann. Chem. *641*, 1 (1961).

[16] *H. Bredereck, R. Gompper, K. Klemm*, and *H. Rempfer*, Chem. Ber. *92*, 837 (1959).

[17] *W. Bauer*, Ph. D. Thesis, Technische Hochschule Stuttgart, 1963.

Some Aspects of the Chemistry of Organoselenium Compounds

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Dedicated to Prof. Dr. Karl Winnacker on the occasion of his 60th birthday

In this article, the gradations in reactivity of organic oxygen, sulfur, and selenium compounds of equivalent structure ("isologues") are reviewed. New or improved methods for the preparation of organoselenium compounds (especially saturated and unsaturated selenides) are described. The addition of selenols onto acetylenic triple bonds leads chiefly to cis-adducts.

1. Introduction

The first organic compounds containing selenium were described [2] a few decades after *Berzelius* [1] had discovered selenium (1818) in the residues from oxidation of sulfur by the lead chamber process worked at Gripsholm. Although their number increased rapidly in the time which followed, up to the present organoselenium compounds have not achieved importance equal to that of organosulfur compounds. It is certainly not just their greater inaccessibility nor their often unpleasant handling properties (many organoselenium compounds are highly toxic and have a penetrating odor) which have opposed systematic study, but also their great tendency towards autoxidation and their sensitivity to light. The few detailed reviews of organoselenium compounds, among which those of *Campbell, Walker*, and *Coppinger* [3] and of *Rheinboldt* [4] are especially prominent, show that there are also large gaps from the point of view of method. For example, certain preparative methods frequently apply to only one compound, while their scope is unknown. Systematic studies are still largely lacking, and the numerous articles comparing the reactivity of isologous [*] oxygen and sulfur compounds outnumber by far those which also include organoselenium compounds. Despite the incompleteness of the information available, a short comparative analysis of the reactivity of isologous organic compounds of the elements of Group VI of the periodic table appears to be justified by the recent increase in interest in organoselenium compounds, especially from the biochemical side [5]. This has been combined with a selection of newer or improved methods for preparing organoselenium compounds, especially those which assume a central position (cf. Fig. 1)

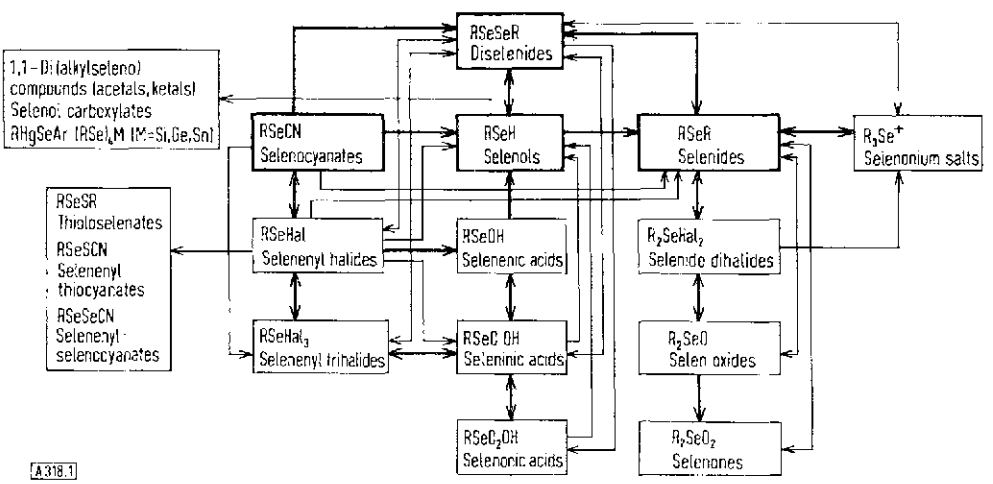


Fig. 1. The more important functional organoselenium compounds: Flow diagram of syntheses.

[*] The term "isologue" is applied to compounds of equivalent structure which differ only by one or more hetero-atoms belonging to the same group in the periodic table.

[1] *J. J. Berzelius*, Afhandl. Fys. Kemi Mineralogi *6*, 42 (1818); Ann. Chim. physique [2], *9*, 160 (1818); cf. *E. M. Weeks*, J. chem. Educat. *9*, 477 (1932); Gmelins Handbuch der anorganischen Chemie. 8th Edit., Springer, Heidelberg 1953, Syst.-No. 10, part A, p. 1.

[2] *F. Wöhler* and *C. Siemens*, Ann. Chem. Pharm. *61*, 360 (1847); *C. A. Joy*, ibid. *86*, 35 (1853); *F. Wöhler* and *J. Dean*, ibid. *97*, 5 (1856); *B. Rathke*, ibid. *152*, 211 (1869); *A. Schröder*, Ber. dtsch. chem. Ges. *4*, 403 (1871).

[3] *T. W. Campbell, H. G. Walker*, and *G. M. Coppinger*, Chem. Reviews *50*, 279 (1952).

[4] *H. Rheinboldt* in *Houben-Weyl*: Methoden der organischen Chemie. 4th Edit., Thieme, Stuttgart 1955, Vol. IX, p. 917.

[5] *K. Schwarz* and *C. M. Foltz*, J. Amer. chem. Soc. *79*, 3292 (1957); *H. Finck*, Naturwissenschaften *47*, 499 (1960); *J. Bremer* and *Yasuo Natori*, Biochim. biophysica Acta *44*, 367 (1960); *H. Zalkin, A. L. Tappel*, and *J. P. Jordan*, Arch. Biochem. Biophysics *91*, 117 (1960); *L. Pichat, M. Herbert*, and *M. Thiers*, Tetrahedron *12*, 1 (1961).

because of their flexibility as intermediates in the synthesis of important saturated and unsaturated selenides.

2. Comparison of the Reactivities of Isologous Organic Compounds of Group VI Elements

a) The Inductive Effect of the Hetero-Atoms

Baker and *Moffitt* have reviewed the isomers formed by mononitration of isologous phenyl- and benzyl-trimethyl- and -dimethyl-onium salts [6]. They showed that the yield of *meta*-nitrated product decreases with increasing atomic weight within any group and increases with increasing atomic weight within any period of the periodic table; see Table 1. Purely *meta*-nitration of the

Table 1. Quantity of *meta*-nitro product obtained on nitration of compounds of types *(1)* and *(2)* in relation to the kind of hetero-element A.

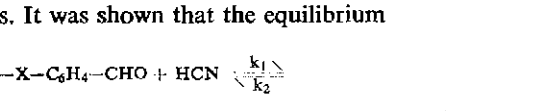
(1) *(2)*

A	*m*-Nitro-*(1)* [%]	*m*-Nitro-*(2)* [%]	A	*m*-Nitro-*(1)* [%]	*m*-Nitro-*(2)* [%]
N	100	88	O	100	
P	100	10.1	S	100	52
As	98.2	3.5	Se	100	16
Sb	86				

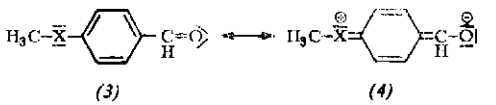
phenyl compounds *(1)* containing Group VI elements was observed and attributed by the authors to localization of the hetero-atom's free electron pair. The considerable alteration in the proportions of the isomers on proceeding to the benzyl derivatives *(2)* shows how much a methylene group changes the inductive effect of the hetero-atoms and hence the course of reaction.

b) The Mesomeric Effect of the Hetero-Atoms

The formation of cyanohydrins of aromatic aldehydes of the type *m*- and *p*-$H_3C-X-C_6H_4-CHO$ (X = O, S, or Se) was used by *Baker*, *Barrett*, and *Tweed* [7] to study the influence of the mesomeric effect upon the reactivity of isologous compounds of Group VI elements. It was shown that the equilibrium



is influenced by the +M effect of the hetero-atoms, since this leads to more or less large resonance stabilization of the *para*-substituted compounds [limiting structures *(3)* and *(4)*].



(3) *(4)*

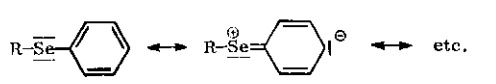
A greater resonance stabilisation requires a higher activation energy for the addition of the hydrogen cyanide, *i.e.* a smaller velocity of cyanohydrin formation (k_1) is observed. If the equilibrium in the reaction of unsubstituted benzaldehyde with hydrogen cyanide is taken as a standard, then any increase of $K = k_2/k_1$ indicates that the hetero-atom is exerting a +M effect. If it is assumed with *meta*-substituted aldehydes that the inductive effect of the substituents essentially controls variations in the result of the reaction, then the ratio K_{para}/K_{meta} (Table 2) gives a measure of the +M effect of X (=O, S, Se).

The same authors obtained similar results [8] from the dissociation constants of isologous aromatic carboxylic acids of the type *m*- and *p*-$H_3C-X-C_6H_4-COOH$ (X = O, S, or Se). Here the ratio K_{para}/K_{meta} (related to unsubstituted benzoic acid) was regarded as a measure of the relative size of the +M effect exerted by the hetero-atoms (Table 2).

Table 2. Ratios of the equilibrium constants K_{para}/K_{meta} for the cyanohydrin reaction of substituted aromatic aldehydes and of the dissociation constants K_{meta}/K_{para} for substituted benzoic acids; the numbers indicate relative (not absolute) values.

p- or *m*-substituent	K_{para}/K_{meta} for cyanohydrin formation	K_{meta}/K_{para} for dissociation
H	1	1
H_3C-O-	10.05	2.5
H_3C-S-	9.36	1.87
H_3C-Se-	8.98	1.85

The results of studies of the dipole moments of isologous organic compounds of Group VI elements [9] are in agreement with the kinetic data. They show that the resonance of the unbound $4(p_z)^2$ electron pair of selenium with the π-electron system of the benzene ring among the limiting structures *(5)*, *(6)*, *etc.* is weaker



(5) *(6)*

than that of the oxygen and sulfur isologues. The "π-moments" proportional to such a resonance effect are, for example, 0.9 D for anisole, 0.5 D for methyl phenyl sulfide, and 0.4 D for methyl phenyl selenide. Further-

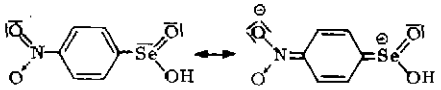
[6] *J. W. Baker* and *W. G. Moffit*, J. chem. Soc. (London) *1930*, 1722; *A. Pollard* and *R. Robinson*, ibid. *1930*, 1765; *D. Vorländer* and *K. Büchner*, Ber. dtsch. chem. Ges. *58*, 1898 (1925); *C. K. Ingold* and *E. H. Ingold*, J. chem. Soc. (London) *1928*, 2249; *R. J. W. Le Fèvre*, ibid. *1929*, 2771.

[7] *J. W. Baker*, *G. F. C. Barrett*, and *W. T. Tweed*, J. chem. Soc. (London) *1952*, 2831.

[8] *J. W. Baker*, *G. F. C. Barrett*, and *W. T. Tweed*, J. chem. Soc. (London) *1952*, 2833.

[9] *J. E. Coop* and *L. E. Sutton*, J. chem. Soc. (London) *1938*, 1869; *M. T. Rogers* and *T. W. Campbell*, J. Amer. chem. Soc. *69*, 2039 (1947); *70*, 1029 (1948); *L. Chierici*, *H. Lumbroso*, and *R. Passerini*, C. R. hebd. Séances Acad. Sci. *237*, 611 (1953); *L. Chierici*, *H. Lumbroso*, and *R. Passerini*, Bull. Soc. chim. France *1955*, 22, 686; *H. Lumbroso* and *G. Dumas*, ibid. *1955*, 651; *H. Lumbroso*, ibid. *1955*, 648; Boll. Sci. Fac. Chim. Ind. Bologna, *19*, 1 (1961).

more, *Gould* and *McCullough* [10] have pointed out that a plot of the log k values of the dissociation constants of substituted benzeneseleninic acids (including the *p*-nitro compound) against the Hammett σ-constants results in a straight line. This indicates only a small degree of resonance of the outer electrons of the selenium atom with the benzene ring [11].



c) Formation of Onium Salts

Our own studies were intended to clarify the effect of polar substituents on the charge density at the hetero-atoms and the manner in which such an effect is transferred across the hetero-atoms to neighboring reactive sites.

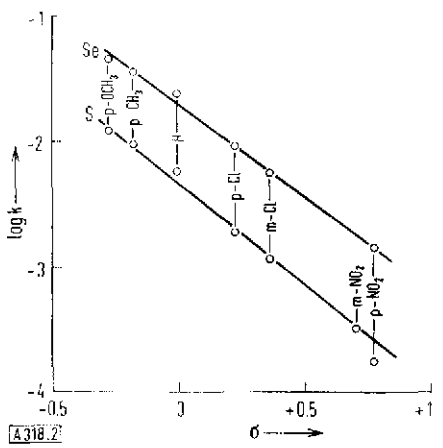


Fig. 2. Log k = f(σ) for the formation of onium salts from isologous alkyl aryl sulfides and selenides with dimethyl sulfate in benzyl alcohol at 45.2 °C.

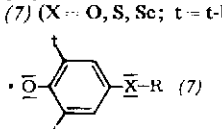
ρ(Sulfide): −1.14 ρ(Selenide): −1.32

A kinetic study of the formation of sulfonium and selenonium salts by addition of dimethyl sulfate onto isologous 3- and 4-substituted methyl phenyl sulfides and selenides showed that the nucleophilic character of sulfur and selenium is almost equally susceptible in each case to the effect of polar substituents. This is a result of the nearly parallel regression lines obtained by plotting the values of log k for the above reaction against Hammett's σ-constants (Fig. 2).

The diagram illustrates the fact that selenides have considerably greater nucleophilicity than the isologous sulfides [12].

[10] *E. S. Gould* and *J. D. McCullough*, J. Amer. chem. Soc. *73*, 1109 (1951).

[11] With regard to the mesomerism of isologous radicals of typ *(7)* (X = O, S, Se; t = t-butyl), cf. *E. Müller, K. Ley, K. Scheffler,*



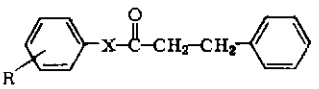
(7)

and *R. Mayer*, Chem. Ber. *91*, 2682 (1958); *K. Scheffler*, Z. Elektrochem., Ber. Bunsenges. physikal. Chem. *65*, 439 (1961); *E. Müller, H. B. Stegmann*, and *K. Scheffler*, Liebigs Ann. Chem. *645*, 79 (1961); *657*, 5 (1962).

[12] *J. Gosselck* and *H. Barth*, Z. Naturforsch. *16b*, 280 (1961).

d) Hydrolysis of Isologous Phenyl Esters

We have answered the question as to how substituent effects are transferred across hetero-atoms to a neighboring reaction site by studying the alkaline hydrolysis of the isologous phenyl β-phenylpropionates *(8)* [13, 14]. The rate constants for hydrolysis of the three isologous ester groups provide a relative measure of the differences in reactivity conferred by the hetero-atoms. On the



(8), X = O, S, Se

other hand, within any single group of esters, the rate constants represent the polar effects of substituents R in the phenoxy, phenylthio, or phenylseleno group upon the reaction centre. The fact that the Hammett lines are parallel shows that polar substituent effects are absorbed and transferred in the same way by oxygen, sulfur, and selenium atoms [13]. Obviously the different electronegativities (O = 3.5; S = 2.5; Se = 2.4) [15] and polarizabilities of the hetero-atoms are not called into play in the above reaction; although all hydrolyses take place with X-acyl fission (X = O, S, or Se; see Fig. 3), it turns out that the sequence within the three groups (Se≫O>S) is the opposite of that of the bond energies (E_{C-O} = 85.5, E_{C-S} = 65, E_{C-Se} = 58 kcal/mole) [16]. It remains to be seen to what extent the mechanism is influenced here by solvation and steric effects.

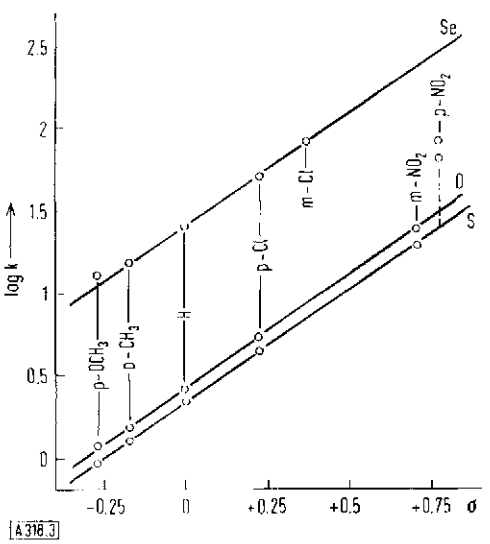


Fig. 3. Log k = f(σ) for the alkaline hydrolysis of isologous substituted phenyl β-phenylpropionates in 70 % aqueous acetone at 0 °C.

ρ(phenyl β-phenylpropionates): + 1.46
ρ(phenyl β-phenylthiopropionates): + 1.46
ρ(phenyl β-phenylselenopropionates): + 1.47 [17]

[13] *J. Gosselck, H. Barth*, and *L. Béress*, Liebigs Ann. Chem., in the press.

[14] With regard to investigations on isologous O- and S-esters, cf. *E. Tommila* und *C. N. Hinshelwood*, J. chem. Soc. (London) *1938*, 1804; *J. R. Schaefgen*, J. Amer. chem. Soc. *70*, 1308 (1948); *H. Böhme* and *H. Schran*, Chem. Ber. *82*, 452 (1949); *P. N. Rylander* and *D. S. Tarbell*, J. Amer. chem. Soc. *72*, 3021 (1950).

[15] *L. Pauling:* The Nature of the Chemical Bond. 3rd Edit., Cornell University Press, Ithaca, N.Y. 1960, p. 90.

[16] *T. L. Cottrell:* The Strengths of the Chemical Bond. 2nd Edit., Butterworths, London 1958, pp. 275–276.

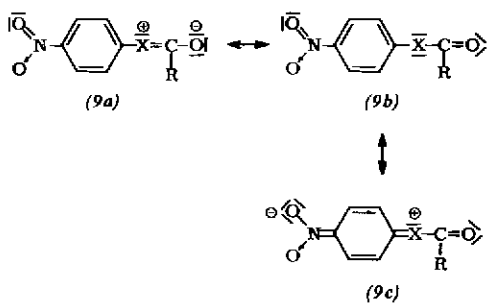
The hydrolyses were carried out in 70 or 80 % aqueous acetone at 0 and −16.5 °C. Even the hydrolysis of 4-nitrophenyl β-phenylselenopropionates can be followed kinetically at the lower temperature although it is complete within a few seconds at 0 °C. If the usual σ-value for a 4-nitro group (+ 0.778) was inserted as Hammett constant [18] (which, however, did not allow for resonance of the 4-nitro group with the reaction centre or with electrons capable of resonance belonging to other atoms [19]), the measurements in every series of experiments invariably led to an almost equal distance ("resonance parameter") of the O-, S-, and Se-esters from the lines of regression. The σ-values corrected to fit the lines then amount to:

σ(4-nitrophenyl β-phenylpropionate): +1.08

σ(4-nitrophenyl β-phenylthiopropionate): +1.05

σ(4-nitrophenyl β-phenylselenopropionate): +1.02

The σ-value for 4-nitrophenyl β-phenylthiopropionate almost coincides with that which describes the reactivity of 4-nitrothiophenol (+ 1.04) [20]. It can therefore be assumed that the same inductive and mesomeric effects are in operation during the hydrolysis of these esters as determine the reactivity of 4-nitrothiophenol, and that participation of the carbonyl group in the resonance system [limiting structure *(9a)*] is of only minor importance.



(9a) *(9b)* *(9c)*

The somewhat lower value for 4-nitrophenyl β-phenylselenopropionate (σ = +1.02) is in agreement with the findings of other authors already mentioned. A less favorable weighting of the limiting structure *(9c)* in comparison to the S-isologue may be interpreted in terms of the double bond rule [21]. On the other hand, the value found for 4-nitrophenyl β-phenylpropionate (+1.08) lies considerably below the value derived from the reactivity of 4-nitrophenol (+1.27); this indicates a charge distribution corresponding to predominance of the limiting structure *(9a)* with the relatively basic carbonyl oxygen atom.

e) Basicity of the Carbonyl Group in Isologous Esters

In order to determine the differences in the relative charge densities at the carbonyl oxygen atom of oxygen, sulfur, and selenium esters, we have carried out basicity measurements [24] according to a method developed by *Cook* [22] and by *Baker* and *Harris* [23]: the stronger the intermolecular hydrogen bond between the carbonyl oxygen atom and a compound containing an acidic CH group (we used phenylacetylene), the lower the wave numbers at which the new band appears in the spectrum for the associated CH group ($\nu_{CH\text{-}ass.}$) relative to the absorption band for the free CH group ($\nu_{CH\text{-}unass.}$). The difference $\nu_{CH(unass.)}-\nu_{CH(ass.)}$ then gives a relative measure of the basicity. The results of our own measurements corresponded with the comparable figures of other authors. Figure 4 clearly shows the relatively high basicity of the O-esters, although the Se-isologues still come before the S-isologues.

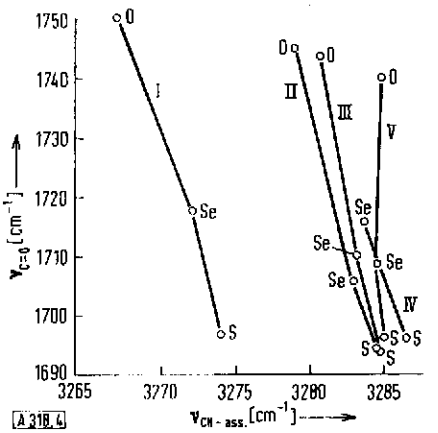


Fig. 4. Relationship between the basicity of the carbonyl oxygen atom and the position of the carbonyl bond vibration frequency ($\nu_{C=O}$) in the spectra of isologous esters (X = O, S, or Se); the smaller the value of $\nu_{CH\text{-associated}}$ the greater the basicity.

(I) = $H_3C-X-CO-CH_3$; (II) = $H_3C-X-CO-CH_2-C_6H_5$;
(III) = $H_3C-X-CO-(CH_2)_2-C_6H_5$; (IV) = $C_6H_5-CH_2-X-CO-CH_3$;
(V) = $C_6H_5-CH_2-X-CO-(CH_2)_2-C_6H_5$

The studies of the infrared spectra also showed that the polar substituent effects were also taken over and transferred equally well by the hetero-atoms in the lower excited states. Thus, when the carbonyl frequencies ($\nu_{C=O}$) of isologous substituted phenyl β-phenylpropionates are plotted against the Hammett constants, parallel lines are also obtained. It

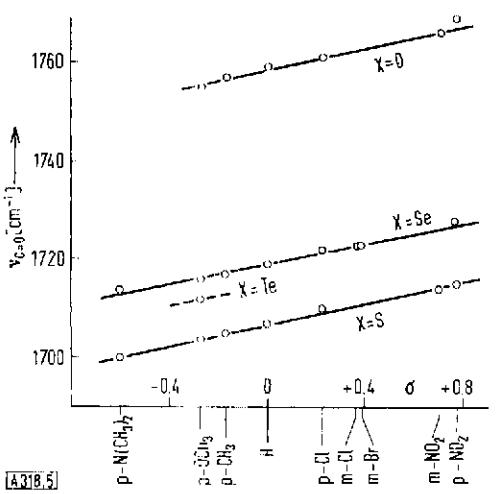


Fig. 5. C=O Vibration frequencies of esters of type *(8)*.

[17] Disregarding the 4-methoxy substituent, cf. *G. Kresze, W. Schramm*, and *G. Clewe*, Chem. Ber. *94*, 2066 (1961).

[18] *L. P. Hammett*, J. Amer. chem. Soc. *59*, 96 (1937); Trans. Faraday Soc. *34*, 156 (1938); *H. H. Jaffé*, Chem. Reviews *53*, 191 (1953); *J. Hine:* Reaktivität und Mechanismus. Thieme, Stuttgart 1960, S. 71.

[19] *M. S. Newman:* Steric Effects in Organic Chemistry. Wiley, New York 1956, pp. 576–578.

[20] *H. H. Jaffé*, Chem. Reviews *53*, 228, 229 (1953); *H. A. Staab:* Einführung in die theoretische organische Chemie. Verlag Chemie, Weinheim 1959, p. 585.

[21] *G. Baddeley*, J. chem. Soc. (London) *1950*, 663; *J. Gosselck*, Chem. Ber. *91*, 2347 (1958).

[22] *D. Cook*, J. Amer. chem. Soc. *80*, 49 (1958); *T. L. Brown*, ibid. *80*, 3514 (1958).

[23] *A. W. Baker* and *C. H. Harris*, J. Amer. chem. Soc. *82*, 1923 (1960).

[24] *J. Gosselck* and *J. Meinrenken*, unpublished experiments.

is interesting that the order of the lines does not correspond to that which is to be expected from the electronegativities of the hetero-atoms [25].

The central position of the Se-isologues observed hitherto for all the esters studied [26] is considered to be most probably a result of the superposition of mass effects upon the mesomeric and inductive effects. Regarding the mass effect upon the position of "characteristic" bands, an investigation by *Overend* and *Sherer* [27] may be referred to. Using isologous carbonyl halides of the type X–CO–Y as an example, they showed that the force constant of the C=O bond vibration does not depend solely upon the polar effects exerted by the substituents X and Y, but contains additional constituents originating from the vibrations of the bonds between the carbon and halogen ($K_{(C-X)}$, $K_{(C-Y)}$) and from the deformation vibrations ($D_{(X-C-Y)}$, $D_{(O\ C-Y)}$, $D_{(O-C-X)}$) which also have a steric effect. Superposition of all these forces defines the experimentally observed frequency.

As may be seen from Figure 6, an approximate proportionality exists between the log k values for the hydrolysis of isologous substituted phenyl β-phenylpropionates and the wave numbers of their C=O bond vibrations [28]. The relationships known hitherto between the reactive properties of molecules and their infrared spectra (which can if necessary be called upon for semi-quantitative predictions of the results of reactions [29]) have thus been extended to a vertical group of the periodic table.

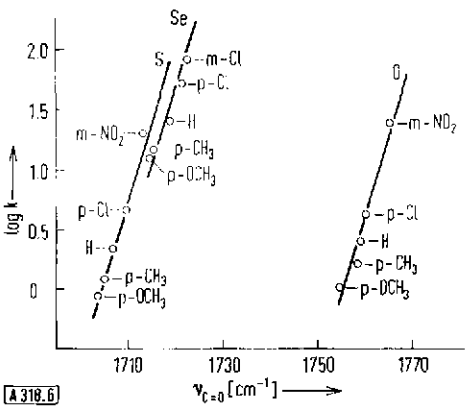


Fig. 6. Values of log k for the alkaline hydrolysis of isologous substituted phenyl β-phenylpropionates of type *(8)* *vs.* the wave numbers of the C=O bond vibrations of these esters.

f) Ultraviolet Absorption of Isologous Compounds

The numerous studies of the absorption of ultraviolet light by isologous organic compounds of Group VI elements cannot be discussed in detail here [30]. However, as a typical case, the bathochromic shift of the absorption bands of longest wavelength of isologous ethers may be referred to here. This increases in the direction O-<S-<Se-isologues. These bands appear as a result of $n \rightarrow \sigma^*$ or $n \rightarrow \pi^*$ transitions of the unbound electron pairs from the hetero-atoms; in the case of unsaturated compounds, $\pi \rightarrow \pi^*$ transitions may be superimposed upon these. The expected transitions are found with open-chain, cyclic, saturated, and unsaturated isologous ethers. They depend upon the excitability of the unbound electron pairs of the hetero-atoms, which becomes greater with increasing atomic weight (decreasing electronegativity). The shifts of the absorption bands of longest wavelength of isologous chromanones *(10)* and chromones *(11)* [Table 3] are, as expected, considerably greater between the oxygen and sulfur isologue than between the sulfur and selenium compounds. The shifts are accompanied by only small variations of intensity.

Table 3. Maxima and intensities of the absorption bands of longest wavelength of isologous chromanones *(10)* and chromones *(11)*.

(10) *(11)*

Compound	λ_{max} [mμ]	log ε
(10), X = O	321	3.62
X = S	346	3.59
X = Se	353	3.54
(11), X = O	298.3	3.88
X = S	334.0	3.99
X = Se	349.0	4.01

3. Relative Electron-Donor Properties of Isologous Ethers and Alcohols

Studies of the coordination compounds of isologous dialkyl ethers with trimethylaluminum as electron acceptor show that the stability of the complexes diminishes in the order O >S>Se>Te [31]. Trimethylgallium has proved to be an especially suitable acceptor which permits comparison of the relative donor proper-

[25] *J. Gosselck*, Z. Naturforsch. *16b*, 404 (1961).

[26] *J. Gosselck* and *J. Meinrenken*, unpublished experiments.

[27] *J. Overend* and *J. R. Sherer*, Spectrochim. Acta *16*, 773 (1960).

[28] *J. Gosselck*, *H. Barth*, and *L. Béress*, Liebigs Ann. Chem., in the press.

[29] *H. A. Staab*, *W. Otting*, and *A. Ueberle*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *61*, 1000 (1957); *H. A. Staab:* Einführung in die theoretische organische Chemie. Verlag Chemie, Weinheim 1959, pp. 280–282, 590, and references given there; *H. A. Staab*, Angew. Chem. *74*, 409 (1962); Angew. Chem. internat. Edit. *1*, 353 (1962).

[30] *O. Behaghel* and *K. Schneider*, Ber. dtsch. chem. Ges. *60*, 88 (1936); *R. S. Mulliken*, J. chem. Physics *7*, 339 (1939); *M. Nguyen-Quangh Trinh*, C. R. hebd. Séances Acad. Sci. *232*, 2023 (1951); *K. Bowden* and *E. A. Braude*, J. chem. Soc. (London) *1952*, 1068; *J. F. Baker*, *G. F. C. Barrett*, and *W. T. Tweed*, ibid. *1952*, 2834; *G. Milazzo*, Gazz. chim. ital. *82*, 362 (1952); *G. Milazzo* and *L. Paolini*, ibid. *82*, 576 (1952); *I. Chierici* and *R. Passerini*, Rend. Accad. Lincei *8*, 14, 99 (1953); *L. Chierici*, *H. Lumbroso*, and *R. Passerini*, Boll. sci. Fac. Chim. ind Bologna *12*, 127 (1954); *R. Passerini*, J. chem. Soc. (London) *1954*, 2256; *A. Cerniani* and *R. Passerini*, ibid. *1954*, 2261; *G. Bergson*, Arkiv för kemi *13*, 11 (1958); *L. Chierici* and *G. Pappalardo*, Gazz. chim. ital. *89*, 560, 1900 (1959); *G. Milazzo* and *G. DeAlti*, Rend. Ist. super. Sanità *22*, 787 (1959); *L. Chierici* and *G. Pappalardo*, Gazz. chim. ital. *90*, 69 (1960); *A. Bellotti* and *I. Chierici*, ibid. *90*, 1125 (1960); *G. Modena*, Adv. molecular Spectroscopy *1962*, 483; cf. *H. A. Staab:* Einführung in die theoretische organische Chemie. Verlag Chemie, Weinheim 1959, p. 308; *J. Gosselck* and *E. Wolters*, unpublished experiments.

[31] *N. Davidson* and *H. C. Brown*, J. Amer. chem. Soc. *64*, 316 (1942); *G. E. Coates*, J. chem. Soc. (London) *1951*, 2003.

ties of isologous ethers and alcohols. Measurements of the dissociation of the complex $(H_3C)_3\overset{\ominus}{G}a-\overset{\oplus}{X}-(CH_3)_2$ (X = O, S, Se, or Te) in the vapor phase revealed the order of stability O > Se > S ~ Te [32] (Table 4).

Table 4. Dissociation of complexes of the type $(H_3C)_3\overset{\ominus}{G}a-\overset{\oplus}{X}-(CH_3)_2$ at 100 °C in the vapor phase.

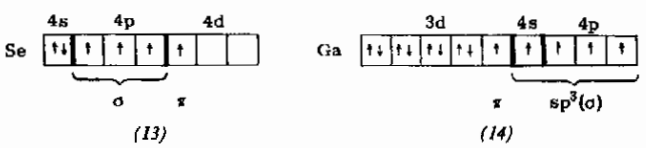
X	Degree of dissociation [%]	Heat of dissociation (−ΔH) [kcal/mole]
O	70	9
S	90	8
Se	78	10
Te	90	8

According to the qualitative ideas developed by *Coates*, the coordination compounds of the O-isologues – *e.g.* with boron, aluminum, or gallium trialkyls – should be due principally to the electrostatic attraction between the charge cloud around the oxygen atom and the positive centre of the acceptor. On the other hand, the donor-acceptor interaction in the case of complexes with atoms of the later groups in the periodic table is determined to a considerable extent by resonance between the "true" coordinative limiting structure $(\overset{\ominus}{A}-\overset{\oplus}{B})$ and the covalent canonical form (A=B) resulting from incorporation of the d-orbitals into the double bond. Thus the charge distribution in the coordination compound formed, for example, from trimethylgallium and dimethyl selenide can be described by the limiting structures *(12a)* and *(12b)*.

$$(CH_3)_3\overset{\ominus}{G}a-\overset{\oplus}{S}e(CH_3)_2 \longleftrightarrow (CH_3)_3Ga{=}Se(CH_3)_2$$

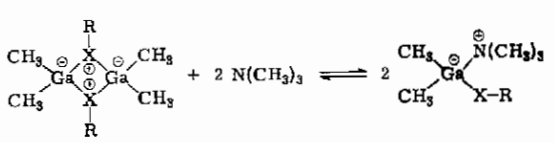
(12a) *(12b)*

The electron configurations *(13)* and *(14)* are assumed for the form *(12b)*.



(13) *(14)*

The dimers of the type *(15a)*, where X = O, S, or Se, obtained from the isologous alcohols and trimethylgallium are not markedly dissociated in the vapor phase below 170 °C. Unlike its less stable sulfur and selenium isologues (X = S or Se; R = CH_3), the compound obtained from methanol (X = O, R = CH_3) does not undergo the following replacement reaction with trimethylamine.



(15a) *(15b)*

[32] *G. E. Coates*, J. chem. Soc. (London) *1951*, 2003.

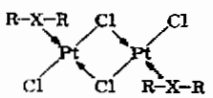
Trimethylgallium also forms analogous dimers with phenols, thiophenol, and selenophenol, *e.g.* $[(CH_3)_2Ga-SeC_6H_5]_2$. Replacement by trimethylamine occurs with all the coordination compounds containing aryl groups. *Coates* [33] measured the dissociation vapor pressure of this kind of trimethylamine adduct and correlated it with the donor properties of the RX-residue (X = O, S, or Se; R = CH_3, phenyl, or substituted phenyl). As is evident from Table 5, the donor character of the hetero-atoms decreases in the order O > S > Se with both the phenyl-substituted and the methyl-substituted adducts. Replacement of a methyl group by a phenyl group also leads to reduction of the dissociation vapor pressure.

The oxygen atom in the t-butylphenoxy group is a stronger donor than that in the phenoxy group; the donor activity is reduced by substitution with chlorine.

Table 5. Dissociation vapor pressures for the compounds $(CH_3)_2Ga(O-XR)N(CH_3)_3$ at 20 °C [33].

−XR	p [mm]	−XR	p [mm]	−XR	p [mm]
$-O-CH_3$	No adduct	$-O-C_6H_4$-t-C_4H_9	14	$-O-C_6H_5$	6.1
$-S-CH_3$	10.3–10.4	$-O-C_6H_4-Cl-p$	1.5	$-S-C_6H_5$	0.4
$-Se-CH_3$	4.5			$-Se-C_6H_5$	0.1–0.2

Chatt and *Venanzi* [34] found that the stability of the coordination compounds of platinum(II) chloride with isologous alkyl ethers diminishes in the sequence S > Te > Se.



(16), X = O, S, Se; R = CH_3, C_2H_5, C_3H_7

As in the case of the addition of alkyl halides and dimethyl sulfate onto isologous ethers (leading to sulfonium, selenonium, and telluronium salts), here the oxygen isologues prove to be practically incapable of forming stable compounds. This is also evident from an investigation of the stability of the complexes of isologous sulfonated aromatic ethers with silver cations. In Table 6, the logarithms of the first stability constants (log K_1) are reproduced; these are regarded as a measure of the affinities of the ligands for the silver ions [35].

Table 6. Logarithms of the first stability constants K_1 (in l/mole) for complexes of sulfonated isologous ethers with Ag^+ ions at 25 °C.

Ligand	Ion concentration [mole/l]	log K_1
$C_6H_5SO_3^{\ominus}$	1.0	0.04 [*]
p-$H_3CO-C_6H_4-SO_3^{\ominus}$	1.0	0.12 [*]
p-$H_5C_2S-C_6H_4-SO_3^{\ominus}$	0.1	2.62
p-$H_5C_2S-C_6H_4-SO_3^{\ominus}$	0.2	2.59
p-$C_6H_5-S-C_6H_4-SO_3^{\ominus}$	0.1	1.67
d-$C_6H_5-S-C_6H_4-SO_3^{\ominus}$	0.2	1.67
p-$C_6H_5-Se-C_6H_4-SO_3^{\ominus}$	0.1	2.63

[*] Donor probably an oxygen atom of the $SO_3^{\ominus}$ group.

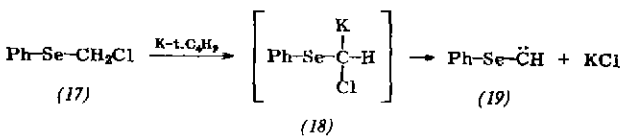
[33] *G. E. Coates:* Organo-Metallic Compounds. 2nd Edit., Methuen, London, Wiley, New York 1960, pp. 149–150.

[34] *J. Chatt* and *L. M. Venanzi*, J. chem. Soc. (London) *1955*, 2787.

[35] *S. Ahrland, J. Chatt, N. R. Davies*, and *A. A. Williams*, J. chem. Soc. (London) *1958*, 264.

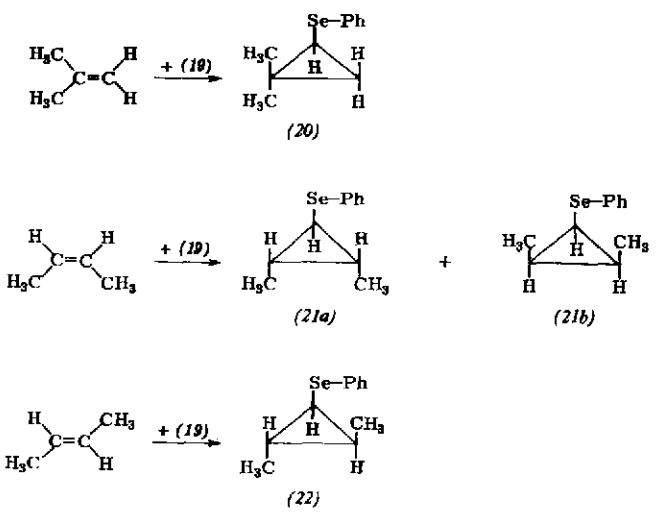
4. Carbenes Containing Selenium

Carbenes containing selenium were obtained for the first time recently by *Schöllkopf* and *Küppers* [36] from the reaction of potassium t-butoxide with chloromethyl phenyl selenide *(17)*, which was obtained from selenophenol, concentrated hydrochloric acid, and formaldehyde. Phenylselenocarbene *(19)* which is probably formed by way of phenylselenochloromethylpotassium *(18)*, is obtained and undergoes stereospecific addition onto olefinic double bonds.



(17) *(18)* *(19)*

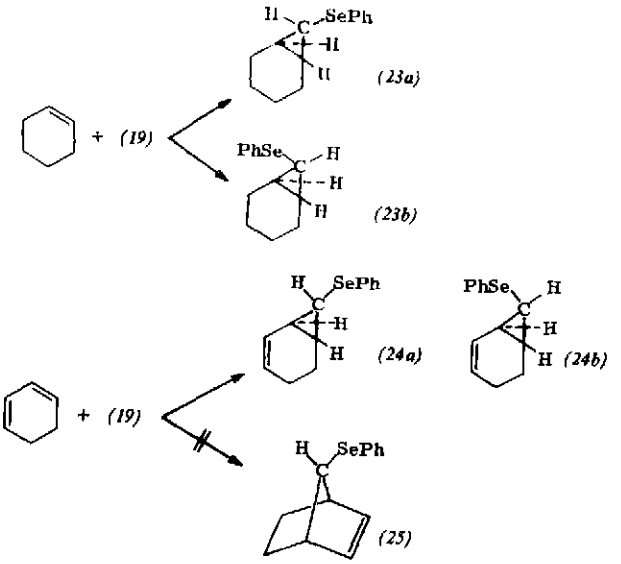
If the reaction is carried out in isobutene, then 1,1-dimethyl-2-phenylselenocyclopropane *(20)* is formed. With *cis*- and *trans*-2-butene, the authors obtained the isomeric cyclopropanes *(21a)*, *(21b)*, and *(22)* in good yield by stereospecific *cis*-addition.



(20) *(21a)* *(21b)* *(22)*

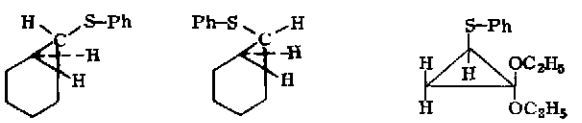
With cyclohexene, phenylselenocarbene afforded a total yield of 70% of a mixture of *exo*- and *endo*-7-phenylselenonorcaranes *(23a)* and *(23b)* in the proportion 2:1, although the assignment of configuration is not yet certain. The *exo*-configuration *(23a)* is assigned to the isomer obtained in greater quantity on the assumptions that the reaction is kinetically controlled and that the transition state leading to the *cis*-isomer has the higher energy. If cyclohexadiene is employed as co-reactant, then geometrically isomeric 7-phenylselenonorcar-5-enes *(24a)* and *(24b)* are obtained in a (total) yield of 68%; here, too, the *exo*-:*endo*- ratio is 2:1. From the fact that 7-phenylselenonorborn-2-ene *(25)* was not found among the products of the reaction, the authors deduced that the carbene adds on preferentially in the 1,2-position.

The aroxy-, alkoxy-, arylthio-, and alkylthiocarbenes prepared by *Schöllkopf* and coworkers in the same or similar ways also undergo stereospecific *cis*-addition onto olefinic double bonds [37]. For example, the phenylthiocarbene obtained by metalation of chloromethyl phenyl sulfide with butyl-



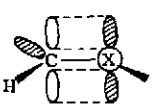
(23a) *(23b)* *(24a)* *(24b)* *(25)*

lithium reacts with cyclohexene to give the corresponding geometrically isomeric 7-phenylthionorcaranes *(26a)* and *(26b)*; with ketene diethylacetal, 1,1-diethoxy-2-phenylthiocyclopropane *(27)* is formed in 80% yield.



(26a) *(26b)* *(27)*

In support of the interpretation of singlet configurations for carbene and dibromocarbene by *Skell* and *Woodworth* [38], the authors discuss the possibility of resonance stabilization of the isologous carbenes by formation of a p_π–p_π bond as a result of overlapping of the empty p-orbitals of the central atom by a filled p-orbital of the ligand *(28)*.



(28), X = O, S, Se

5. New Methods for the Preparation of Organic Selenides

A method discovered by *Hölzle* and *Jenny* can be used to prepare saturated and α,β-unsaturated selenides [39]. Arylselenenyl acetates *(30)* add onto non-polar or weakly polarized olefinic double bonds to give selenides of type *(31)*. The arylselenenyl acetates are formed from areneselenenic esters *(29)* in the presence of acetic acid, and generally need not be isolated [40].

[36] *U. Schöllkopf* and *H. Küppers*, Tetrahedron Letters *1963*, 105.

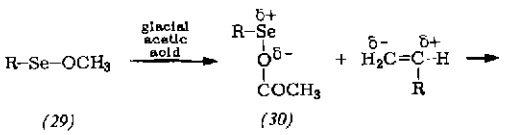
[37] *U. Schöllkopf* and *A. Lerch*, Angew. Chem. *73*, 27 (1961); *U. Schöllkopf*, *A. Lerch*, *W. Pitteroff*, and *G. J. Lehmann*, ibid. *73*, 765 (1961); *U. Schöllkopf*, *A. Lerch*, and *W. Pitteroff*, Tetrahedron Letters *1962*, 241; *U. Schöllkopf* and *G. Lehmann*, ibid. *1962*, 165.

[38] *P. S. Skell* and *R. C. Woodworth*, J. Amer. chem. Soc. *78*, 4496 (1956); *R. C. Woodworth* and *P. S. Skell*, ibid. *81*, 3383 (1959).

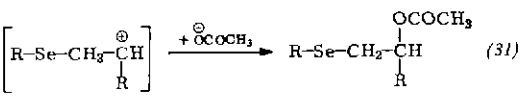
[39] *G. Hölzle* and *W. Jenny*, Helv. chim. Acta *41*, 593 (1958).

[40] *G. Hölzle* and *W. Jenny*, Helv. chim. Acta *41*, 331 (1958).

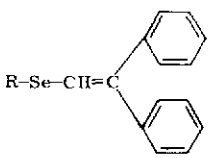
However, if the selenenyl acetate is allowed to act on more strongly polarized olefins, *e.g.* 1,1-diphenylethylene, then substitution products of type *(32)* are obtained.



(29) *(30)*



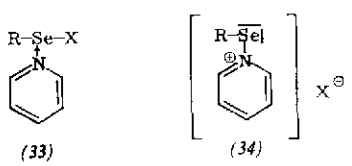
(31)



(32)

If the acetic acid is replaced by pyridine, then not only is the tendency of the selenenyl acetates to substitute enhanced, but arylselenenyl bromides and, on brief warming, arylselenocyanates also react instantaneously in the same way. As in the addition reaction, substitution takes place by initial electrophilic attack on the negatively polarized methylene group of the ethylene; a proton is then eliminated and replaced by the arylseleno group. The accelerating effect of pyridine upon the reaction is attributed to loosening of the Se–X bond by formation of an addition complex *(33)* or an ionic intermediate *(34)*. This was also observed during the preparation of sulfenic esters from sulfenyl chlorides and alcohols [41].

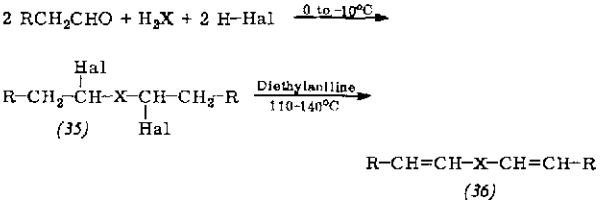
The substitution reactions of the selenenyl acetates and selenocyanates cannot be extended to sulfenic esters or to thiocyanates, and thus form an example of the difference in behavior which is frequently observed between isologous S- and Se-compounds.



(33) *(34)*

(X = $^{\ominus}OCOCH_3$, $CN^{\ominus}$, $Br^{\ominus}$)

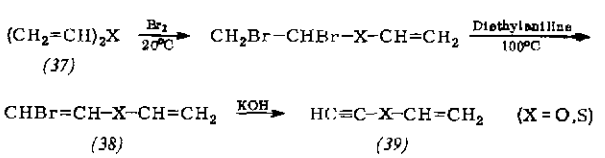
Brandsma and *Arens* obtained isologous divinyl ethers and alkylated divinyl ethers by passing hydrogen sulfide or hydrogen selenide and anhydrous hydrogen halide simultaneously into aldehydes [42]. The α,α′-dihalogeno-thioethers and selenoethers *(35)* initially obtained lose hydrogen halide in the presence of diethylaniline to give di-(2-alkylvinyl) sulfides and selenides *(36)*. The yields lie between 40 and 50 %.



(35) *(36)*

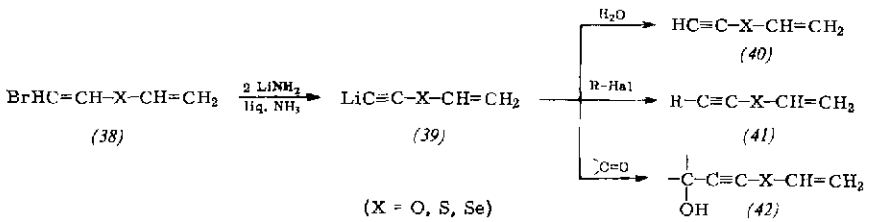
R = H, CH_3, C_2H_5; X = S, Se; Hal = Cl, Br

2-Bromovinyl vinyl ether and 2-bromovinyl vinyl sulfide *(38)* are obtained by bromination and dehydrobromination of divinyl ether and divinyl thioether *(37)*, respectively. Hydrogen bromide is eliminated from the ethers *(38)* by heating with powdered potassium hydroxide, so that vinyloxy- and vinylthioethynes *(39)* are formed [43]. Dehydrobromination of 2-bromovinyl vinyl selenide resulted in only small yields of the desired selenium isologue.



(37) *(38)* *(39)*

Dehydrobromination of isologous bromovinyl vinyl ethers *(38)* with lithium amide in liquid ammonia resulted in considerable improvement and extension of the procedure.



(38) *(39)* *(40)* *(41)* *(42)*

(X = O, S, Se)

Hydrolysis of the lithium derivative of ethynyl vinyl ether *(40)* obtained in this case leads to free ethynyl vinyl ether *(39)*; with alkyl halides, *(40)* can be converted into alkynyl vinyl ethers *(41)*, and with ketones into carbinols *(42)*. The yields of ethers lie between 50 and 70 % for the S- and Se-isologues.

The C≡C bond vibrations of isologous ethynyl vinyl ethers are interesting because they present a case similar to that described above of the C=O bond vibrations of isologous esters, for their frequencies too do not reflect the electronegativities and atomic weights of the hetero-atoms (Table 7). In the laboratory of

Table 7. Position of the C=C- and C≡C-valence vibrations of isologous vinyl ethynyl ethers of type *(40)*.

X in *(40)*	$\nu_{C=C}$ [cm^{-1}]	$\nu_{C\equiv C}$ [cm^{-1}]
O	2290	1630
S	2200	1580
Se	2200	1600

[41] *N. Kharasch, D. P. McQuarrie,* and *C. M. Buess,* J. Amer. chem. Soc. *75*, 2658 (1953).

[42] *L. Brandsma* and *J. F. Arens,* Rec. Trav. chim. Pays-Bas *81*, 34 (1962).

[43] *L. Brandsma* and *J. F. Arens,* Rec. Trav. chim. Pays-Bas *81*, 450 (1962).

Arens, a simple but elegant method for the preparation of ethynyl sulfides, ethynyl selenides, and ethynyl tellurides *(43)* in yields of 50–70 % was also developed [44]. Sodium acetylide is first prepared from acetylene and sodamide and alkylated: finely-powdered sulfur or amorphous selenium or tellurium is then added in small portions and the sodium salt obtained is immediately alkylated. The whole reaction sequence is carried out in liquid ammonia and has the advantage that preliminary preparation of thiols or selenols is unnecessary.

$$HC{\equiv}CH \xrightarrow[liq.\ NH_3]{NaNH_2} NaC{\equiv}CH \xrightarrow[liq.\ NH_3]{RBr} R{-}C{\equiv}CH \xrightarrow[liq.\ NH_3]{NaNH_2}$$

$$R{-}C{\equiv}C{-}Na \xrightarrow[liq.\ NH_3]{X} R{-}C{\equiv}C{-}X{-}Na \xrightarrow[liq.\ NH_3]{R'Br} R{-}C{\equiv}C{-}X{-}R' \quad (43)$$

(X = S, Se, Te)

Brandsma and *Wijers* [45] succeeded in making considerable improvements to the methods which were usually employed hitherto for the preparation of dialkyl sulfides and selenides and alkyl thiols and selenols, and which as a rule depend upon alkylation of sulfides, disulfides, hydrogen sulfides and their Se-isologues.

They allow alkyl halides to act directly upon solutions of sodium and sulfur, selenium, or tellurium in liquid ammonia. Although only traces of di-t-butyl sulfide, selenide, and telluride are formed from t-butyl bromide under these conditions, primary and secondary halides generally give yields of over 80 %. Thiols and selenols can also be obtained in this way, if the disulfides and diselenides obtained first are cleaved with sodium and the salt formed is acidified after evaporation of the ammonia.

$$2\,Na + 2\,X \xrightarrow[liq.\ NH_3]{} Na_2X_2 \xrightarrow[liq.\ NH_3]{RBr,\,RI} R_2X_2$$

$$\xrightarrow[liq.\ NH_3]{2\,Na} 2\,RXNa \xrightarrow{+H^{\oplus}} RXH \quad (X = S, Se)$$

$$\downarrow R'Br$$

$$R{-}X{-}R' \quad (X = S, Se, Te)$$

The reactivity of the sodium sulfides and selenides increases in the order $Na_2S < Na_2S_2 < Na_2Se < Na_2Se_2$. Good to very good yields (*e.g.* CH_3SH: 69 %, C_2H_5SeH: 86 %) of thiols and selenols are also given by this procedure, which has a wide range of application.

6. Fluorinated Organoselenium Compounds

The action of trifluoroiodomethane upon selenium produces bis-trifluoromethyl selenide *(44)* and bis-trifluoromethyl diselenide *(45)* in a ratio of 1:4. In contrast, with sulfur trifluoroiodomethane yields mainly bis-trifluoromethyl disulfide, plus the tri- and tetrasulfides, but no monosulfide. The selenide *(44)* is stable

$F_3C{-}Se{-}CF_3$ *(44)* $\qquad F_3C{-}Se{-}Se{-}CF_3$ *(45)*

in the presence of water, aqueous alkali, dilute acids, and even in nitric acid, and is only hydrolysed by ethanolic potassium hydroxide at 100 °C.

$$F_3C{-}Se{-}CF_3 \rightarrow CHF_3,\ F^-,\ Se^{2-},\ CO_3^{2-} \quad (44)$$

The compound shows scarcely any basic character owing to the high electronegativity of the two trifluoromethyl groups. It does not give complex compounds with mercuric chloride, nor selenonium salts with alkyl halides, nor selenide dihalides with halogens [46].

However, bis-trifluoromethyl diselenide *(45)* is considerably more reactive. It forms a colorless trichloride $CF_3{-}SeCl_3$ with excess chlorine, and with equimolecular quantities yields the corresponding selenenyl chloride $CF_3{-}Se{-}Cl$. Trifluoromethaneselenenyl bromide is obtained by the action of bromine on *(45)*. Concentrated nitric acid converts *(45)* into trifluoromethaneseleninic acid $CF_3{-}SeO_2H$, which cannot be oxidized to the selenonic acid, however. When shaken with mercury, *(45)* forms the mercuric salt of trifluoromethylselenol $CF_3{-}Se{-}Hg{-}Se{-}CF_3$, which decomposes into trifluoromethylselenol CF_3SeH and *(45)* when heated in the presence of hydrogen chloride. The trifluoromethyl derivatives of selenium are generally more reactive than the isologous sulfur compounds.

7. The Steric Course of Addition of Selenols onto Acetylenic Triple Bonds

Aliphatic and aromatic selenols, as well as hydrogen selenide, add onto C C bonds to form α,β-unsaturated selenides in an exothermic reaction [47]. With regard to its stereospecificity, this kind of addition proceeds largely in the same way as the reactions of organosulfur compounds, *i.e.* in basic media the *cis*-isomers are formed principally or exclusively. The preferential formation of *cis*-isomers on base-catalysed addition of thiols onto acetylenes is attributed by *Truce* and coworkers [48] to the appearance of carbanion intermediates, which are supposed to have some configurational stability, by analogy to the stereoisomerism of the isoelectronic oximes. For electrostatic reasons, the alkylthio residue R'S in intermediate *(46)* is situated as far as possible from the free electron pair of the anionic carbon atom, *i.e.* in the *trans*-position. The protonation

[44] *L. Brandsma, H. Wijers*, and *J. F. Arens*, Rec. Trav. chim. Pays-Bas *81*, 583 (1962); cf. *M. Schmidt* and *V. Potschka*, Naturwissenschaften *50*, 302 (1963).

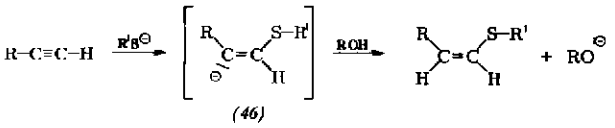
[45] *L. Brandsma* and *H. Wijers*, Rec. Trav. chim. Pays-Bas *82*, 68 (1963).

[46] *J. W. Date, H. J. Emeléus*, and *R. N. Haszeldine*, J. chem. Soc. (London) *1958*, 2939.

[47] *L. Chierici* and *F. Montanari*, Boll. sci. Fac. Chim. ind. Bologna *14*, 78 (1956); *J. Gosselck* and *E. Wolters*, Z. Naturforsch. *17b*, 131 (1962).

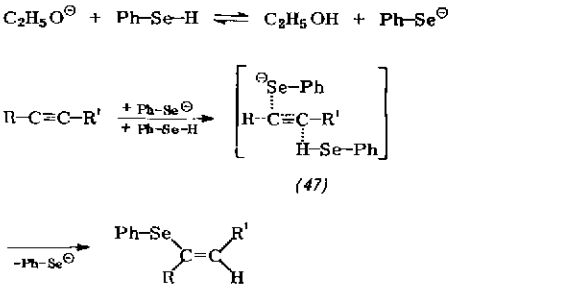
[48] *W. E. Truce, J. A. Simms*, and *M. M. Boudakian*, J. Amer. chem. Soc. *78*, 696 (1956); *W. E. Truce* and *J. A. Simms*, ibid. *78*, 2758 (1956); *W. E. Truce* and *R. F. Heine*, ibid. *81*, 1170 (1959).

by the solvent which immediately ensues therefore leads to the *cis*-adduct.



(46)

Besides this stepwise mechanism, a concerted mechanism has also been proposed, which is also able to explain the predominant formation of the *cis*-isomer. In this mechanism the nucleophilic species and the proton add on simultaneously, but from opposite sides. *Chierici* and *Montanari* [47] also use this interpretation to explain the formation of *cis*-arylselenoacrylic acids on addition of arenecselenols onto propiolic acid. Russian authors [49] believe that the proton comes from the selenol itself and not from the solvent during the addition of phenylselenol onto phenylacetylene and diphenylacetylene [by way of *(47)*].



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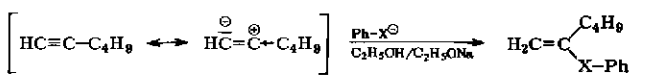
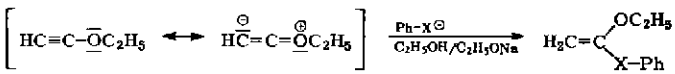


(48) *(50)*, X = S, Se



(49) *(51)*, X = S, Se

In harmony with this interpretation, the 1,2-addition is promoted by electron-attracting substituents (*e.g.* $-C_6H_5$, $-CO-C_6H_5$, $-COOR$, $-COOH$) in the acetylene; conversely, substituents which increase the electron density at the acetylenic carbon atom in the β-position to the substituent by inductive or resonance effects lead to nucleophilic attack of the α-carbon atom by the mercaptides or substituted selenide ions. Thus thiols and selenophenol add onto 1-hexyne *(48)* and ethoxyacetylene *(49)* to form the 1,1-disubstituted ethylenes *(50)* and *(51)*, respectively [50].

It is interesting that selenophenol adds on more stereospecifically in neutral media than thiophenol and at lower temperatures also leads mainly or exclusively to the *cis*-compounds. The isomer ratio is obviously influenced by steric effects, since in the transition state the phenylseleno group shields one side of the β-carbon atom more effectively than the relatively less bulky phenylthio group. In consequence, the proton prefers to approach the molecule from the opposite side.

Table 8 shows the differences in stereoselectivity of the additions of thiophenol and selenophenol onto substituted acetylenes [51].

Table 8. Stereoselectivity of additions of thiophenol and selenophenol onto substituted acetylenes in carbon tetrachloride.

Substrate	Temp. [°C]	Configuration of the adduct	
		with thiophenol	with selenophenol
Phenylacetylene	20	mainly *trans*-	*cis*-
Phenylacetylene	76	*trans*-	*cis*- and *trans*-
Ethyl propiolate	20	*cis*- and *trans*-	mainly *cis*-
Ethyl propiolate	76	mainly *trans*-	mainly *cis*-
Benzoylacetylene	20	mainly *cis*-	*cis*-
Ethoxyacetylene	20	mainly *cis*-	*cis*-

In view of the relatively small bond energy of the Se–C bond, which favors removal of the group containing the selenium on cleavage, there is a possibility that organoselenium compounds may be used for stereospecific syntheses of *cis*-olefins.

This opportunity is taken to thank Professor Winnacker once again for the gift of a "Winnacker Fellowship".

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German version: Angew. Chem. *75*, 831 (1963)

[49] *E. G. Kataev* and *V. N. Petrov*, Zh. obshch. Khim. *32*, 3699 (1962); *L. M. Kataeva*, *L. N. Anonimova*, *L. K. Juldaseva*, and *E. G. Kataev*, ibid. *32*, 3965 (1962).

[50] *J. F. Arens* and *H. J. Alkema*, Rec. Trav. chim. Pays-Bas *79*, 1257 (1960); *H. Volger* and *J. F. Arens*, ibid. *77*, 1170 (1958); *E. Wolters*, Ph.D. Thesis, Universität Gießen, 1963; *E. G. Kataev* and *V. N. Petrov*, Zh. obshch. Khim. *32*, 3699 (1962); *W. E. Truce* and *J. A. Simms*, J. Amer. chem. Soc. *78*, 2757 (1956); *W. E. Truce* and *D. L. Goldhamer*, ibid. *82*, 6427 (1960).

[51] *J. Gosselck* and *E. Wolters*, unpublished experiments.

Preparation of N-Alkoxyureas and Their Use as Selective Herbicides

BY DR. O. SCHERER, DR. G. HÖRLEIN, AND DR. K. HÄRTEL

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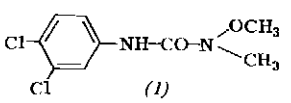
Dedicated to Prof. Dr. Karl Winnacker on the occasion of his 60th birthday

N-(4-Chlorophenyl)-N'-methoxy-N'-methylurea (Aresin®) and N-(3,4-dichlorophenyl)-N'-methoxy-N'-methylurea (Afalon®) are two new herbicides with characteristic selective activity. A simple and convenient method for their preparation is described.

Introduction

N-(4-Chlorophenyl)-*N'*,*N'*-dimethylurea (Monuron) and *N*-(3,4-dichlorophenyl)-*N'*,*N'*-dimethylurea (Diuron) have been known as herbicides for a long time. However, *N*-(3,4-dichlorophenyl)-*N'*-methoxy-*N'*-methylurea *(1)* [Afalon®] and *N*-(4-chlorophenyl)-*N'*-methoxy-*N'*-methylurea *(2)* [Aresin®], which differ only slightly from the former compounds in their chemical constitutions, are nevertheless very different in their general



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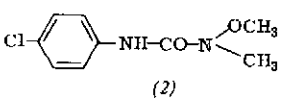


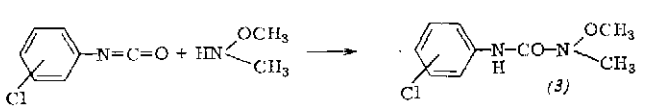
(2)

biological and specific herbicidal properties: Monuron and Diuron are only very weakly selective and persist in the soil for long periods; the analogous methoxy compounds *(1)* and *(2)* show highly selective properties with regard to important cultivated plants and very weak persistence in the soil.

N-Alkoxy-*N*-alkylureas may be prepared by reaction between isocyanates or carbamyl chlorides and alkylhydroxylamines. However, since the last-named compounds are not readily available on the technical scale at present, a more practicable method is the reaction of hydroxylamine and isocyanates followed by alkylation.

1. Addition of O,N-Dimethylhydroxylamines onto Substituted Phenyl Isocyanates

These reactions take place in organic solvents at elevated temperatures [1]. The products *(3)* are generally crystalline, and may be purified if required by recrystallization from petroleum ether.



(3)

[1] German Patent 1028986 (Jan. 17th, 1956), Farbwerke Hoechst AG.; inventors: *O. Scherer* and *P. Heller*.

2. Alkylation of Substituted N-Phenyl-N'-alkoxyureas

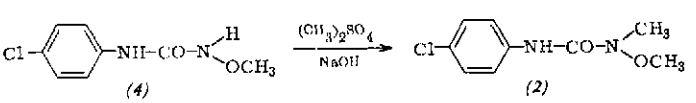
Under identical conditions, *O*-alkylhydroxylamines add onto substituted phenylisocyanates. Alkoxyureas, *e.g. (4)*, are formed which can be purified by recrystallisation from ethyl acetate. Compounds obtainable in this way are shown in Table 1.

Table 1. *N*-Phenyl-*N'*-alkoxyureas R—NH—CO—NH—OR' prepared from *O*-alkylhydroxylamines and phenylisocyanates.

R	R'	M. p. [°C]
Phenyl	CH_3	114—115
4-Chlorophenyl	CH_3	140—142
3-Chlorophenyl	CH_3	119—120
4-Chloro-2-methylphenyl	CH_3	128—129
3,4-Dichlorophenyl	CH_3	138—141
2,4,5-Trichlorophenyl	CH_3	153—154
4-Chlorophenyl	C_2H_5	121—123
4-Chlorophenyl	n-C_3H_7	108—110
Phenyl	n-C_4H_9	84—85
4-Chlorophenyl	n-C_4H_9	94—96

To our knowledge, *N*-alkylation of ureas has not yet been described. In the reactions described in the earlier literature [2], attack has always proceeded at the oxygen atom with the production of *O*-alkylisoureas. The molecular grouping —CO·NH—OR of *N*-alkoxyureas is that of a hydroxamic ester, and according to the literature [3] this grouping always takes part in alkylation reactions in the tautomeric hydroximic acid form —C(OH)=N—OR. In our particular case, therefore, the products expected would be *O*-alkylisoureas.

It was therefore surprising that the alkylation did in fact take place unequivocally and exclusively at the alkoxylated nitrogen atom, with production of the desired *N*-phenyl-*N'*-alkoxy-*N'*-alkylureas, *e.g. (2)*, in high yield.



(4) *(2)*

[2] *E. A. Werner*, J. chem. Soc. (London) *105*, 927 (1914); *P. A. Ongley*, Trans. Roy. Soc. New Zealand *77*, 10 (1948); Chem. Abstr. *39*, 8165 (1945).

[3] *Houben-Weyl:* Methoden der organischen Chemie. 4th Edit., Georg Thieme, Stuttgart 1952, Vol. 8, p. 685.

Alkylation was carried out in suspension in aqueous alkali, or better, in a mixture of aqueous alkali and a hydrophilic organic solvent. *N*-Phenyl-*N'*-alkoxyureas are stable in the presence of alkali [4].

The constitution of the products was shown by the identity of their infrared spectra and mixed melting points with those of compounds prepared by method 1. The method makes it possible to introduce an alkyl residue that is different from that of the alkoxy group, resulting in a wide variety of products, as shown in Table 2.

Table 2. Products $\left(R{-}NH{-}CO{-}N<^{R^1}_{OR^2}\right)$ obtained by alkylation of *N*-phenyl-*N'*-alkoxyureas

R	R^1	Alkylating agent	M.p. [°C] or b.p. [°C/mm]	Action [*] on charlock 0.48 kg/acre	0.24 kg/acre	0.12 kg/acre	0.06 kg/acre	Action [*] on oats 0.48 kg/acre	0.24 kg/acre	0.12 kg/acre	0.06 kg/acre
	$R^2 = CH_3$										
Phenyl	CH_3	Dimethyl sulfate	59–60	5	5	4	3	4	3	2	1
3-Chlorophenyl	CH_3		81–83	5	5	4	3	3	2	1	1
4-Chlorophenyl	CH_3		76–78	5	5	5	5	5	5	4–5	4
3,4-Dichlorophenyl	CH_3		90–91	5	5	5	5	5	4–5	4	3
2,4,5-Trichlorophenyl	CH_3		95–96	4	3	2–3	2	1	0	0	0
2-Methyl-4-chlorophenyl	CH_3		66–67	3	2	1	0	1	1–0	0	0
Phenyl	C_2H_5	Diethyl sulfate	92–93	4–5	3	2–3	2	1–2	1	0–1	0
4-Chlorophenyl	C_2H_5	n-Propyl bromide	90–91	3	2	1	0	2	1	0	0
4-Chlorophenyl	n-C_3H_7	n-Butyl bromide	95–97	2	1	0	0	0	0	0	0
Phenyl	n-C_4H_9		118–120/3	0	0	0	0	0	0	0	0
2-Chlorophenyl	n-C_4H_9		142–145/1	0	0	0	0	0	0	0	0
3-Chlorophenyl	n-C_4H_9		158–165/760	0	0	0	0	1	0	0	0
4-Chlorophenyl	n-C_4H_9		Non-distillable oil	3	2	1	0	0	0	0	0
2,4-Dichlorophenyl	n-C_4H_9		Non-distillable oil	0	0	0	0	0	0	0	0
3,4-Dichlorophenyl	n-C_4H_9		79–80	0	0	0	0	0	0	0	0
2,4,5-Trichlorophenyl	n-C_4H_9		Non-distillable oil	0	0	0	0	0	0	0	0
2-Methyl-4-chlorophenyl	n-C_4H_9		Non-distillable oil	0	0	0	0	0	0	0	0
p-Tolyl	n-C_4H_9		56–58	0	0	0	0	0	0	0	0
4-Chlorophenyl	i-C_3H_7	i-Propyl bromide	93–94	1	0	0	0	0	0	0	0
4-Chlorophenyl	i-C_4H_9 [a]	1-Bromo-2-methylpropane	98–100	0	0	0	0	0	0	0	0
4-Chlorophenyl	s-C_4H_9 [b]	2-Chloro-n-butane	73–75	1	0	0	0	0	0	0	0
4-Chlorophenyl	3-Methyl butyl	1-Chloro-3-methylbutane	41–42	0	0	0	0	0	0	0	0
4-Chlorophenyl	Allyl	Allyl bromide	79–80	3	2	1	0	1	0	0	0
4-Chlorophenyl	3,3-Dichloroallyl	3,3-Dichloroallyl chloride	95–96	0	0	0	0	0	0	0	0
4-Chlorophenyl	Dodecyl	Dodecyl bromide	34–35	0	0	0	0	0	0	0	0
	$R^2 = n\text{-}C_4H_9$										
Phenyl	CH_3	Dimethyl sulfate	138–140/8	1	0	0	0	0	0	0	0
4-Chlorophenyl	CH_3		47–49	1	0	0	0	0	0	0	0

[*] 0 = no damage; 5 = plants killed. [a] = 2-Methylpropyl; [b] = 1-Methylpropyl.

Example

N-(4-Chlorophenyl)-*N'*-methoxyurea (100 g = 0.5 mole) was dissolved in 200 g of 10 % sodium hydroxide solution and 250 ml of methanol, and stirred and cooled in ice-water while 0.6 mole = 75 g of dimethyl sulfate was added dropwise. After stirring for 1 hour at room temperature, *N*-(4-chlorophenyl)-*N'*-methoxy-*N'*-methylurea was obtained in 95 % yield (m.p. 76–78 °C).

[4] German Patent 1076117 (April 17th, 1958) Farbwerke Hoechst AG.; inventors: *O. Scherer, G. Hörlein,* and *R. Hübner.*

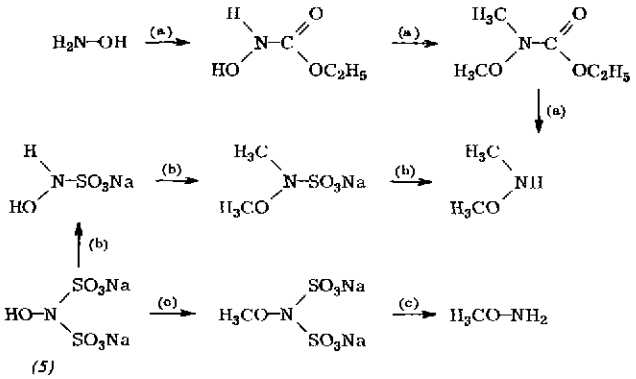
3. Preparation of O-Alkyl- and O,N-Dialkylhydroxylamines

Technically feasible routes were sought for the synthesis of the starting materials for both methods 1 and 2.

O,N-Dimethylhydroxylamine was prepared on the laboratory scale in about 30 % yield by route (a) of Scheme 1 [5]. In the search for other protective groups, the use of sulfo groups, as used in Fremy's salt during the Raschig synthesis of hydroxylamine, was considered. Starting from Fremy's salt *(5)*, hydrolysis of one sulfo group and subsequent methylation and saponification – route (b) – lead to *O,N*-dimethylhydroxylamine in about 30 % yield [6]; alternatively, methylation followed by hydrolysis of both sulfo groups – route (c) – yields

[5] *A. Hantzsch*, Ber. dtsch. chem. Ges. *27*, 1254 (1894); *T. Major, E. E. Fleck*, J. Amer. chem. Soc. *50*, 1, 1479 (1928).

[6] German Patent 1116232 (Nov. 24th, 1959), Farbwerke Hoechst AG., inventors: *O. Scherer* and *G. Schneider.*



(5)

Scheme 1. Synthesis of *O*-alkyl- and *O,N*-dialkylhydroxylamines.

O-methylhydroxylamine in about 50 % yield [7]. The *O*-alkylhydroxylamines shown in Table 3 were prepared by route (c).

Table 3. *O*-Alkylhydroxylamines prepared from Fremy's salt.

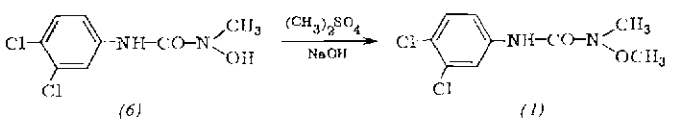
	B. p. [°C]	Alkylating agent	Hydrochloride m. p. [°C]
$H_3C-O-NH_2$	49–50	Dimethyl sulfate	149
$C_2H_5-O-NH_2$	68–69	Diethyl sulfates	128
$n\text{-}C_3H_7-O-NH_2$	90–91	n-Propyl bromide	150–152
$n\text{-}C_4H_9-O-NH_2$	113–115	n-Butyl bromide	152–154

None of the routes mentioned were suitable for use in a technical synthesis. Moreover, some of the alkylated hydroxylamines formed highly explosive mixtures with air and showed strong haemolytic action.

The ethyl methylmethoxycarbamate produced as intermediate in the preparation of *O,N*-dimethylhydroxylamine by route (a), unlike the corresponding methyl or phenyl esters, could not be converted into the desired urea derivative by reaction with chloroaniline.

4. Alkylation of N-Phenyl-N′-alkyl-N′-hydroxyureas

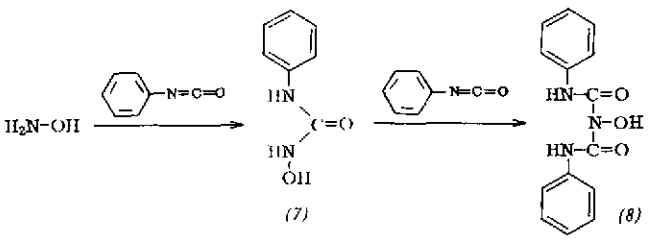
N-Methylhydroxylamine may be prepared by reduction of nitromethane with zinc dust [8] or catalytically with hydrogen over palladium [9]. Its condensation product with phenylisocyanates, *e.g. (6)*, can be methylated to give *N*-alkoxy-*N*-methylureas, *e.g. (1)*.



(6) (1)

5. Alkylation of N-Phenyl-N′-hydroxyureas

Our final resource was to condense hydroxylamine with phenylisocyanates or carbamyl chlorides first (in which case, naturally, only aqueous hydroxylamine can be used) and then to introduce two alkyl groups. Unsubstituted phenylisocyanates can be converted into *N*-phenyl-*N′*-hydroxyurea *(7)* with both anhydrous [10] and aqueous hydroxylamine [11]. The product reacts with further phenylisocyanate to give a compound which can be shown to be *N*-hydroxy-*N′,N″*-diphenylbiuret *(8)* [12].



(7) (8)

However, attempts to condense the more reactive chlorophenylisocyanates with aqueous hydroxylamine resulted in hydrolysis of the isocyanates giving quantitative yields of the symmetrical diphenylureas. The same hydrolytic side reaction takes place on condensation with aqueous amines [13] or in the reaction of carbamyl chlorides with aqueous hydroxylamine [14] and can only be avoided if the reaction is carried out in a two-phase system. In our case the addition of chlorophenylisocyanates onto aqueous hydroxylamine is successfully achieved if the reaction is carried out in a mixture of water and an immiscible organic solvent, *e.g.* chlorinated aliphatic or aromatic hydrocarbons or ethers [15]. Side reactions can be suppressed by maintaining suitable conditions of temperature and pH.

The products (examples in Table 4) give color reactions with Fe^{3+} that are characteristic of hydroxamic acids and produce a black silver mirror with ammoniacal silver nitrate solution.

Table 4. *N*-Phenyl-*N′*-hydroxyureas R–NH–CO–NH–OH prepared from phenylisocyanates and hydroxylamine.

R	Recrystallised from	M. p. [°C]
Phenyl	Butyl acetate	141–143 (decomp.)
4-Chlorophenyl	Ethanol	160 (sinters) 175 (decomp.)
3,4-Dichlorophenyl	Water	126 (sinters) 135 (decomp.)

Despite numerous possible modes of reaction, the alkylation of *N*-phenyl-*N′*-hydroxyureas proceeds in two definite steps. With one mole of alkylating agent, the *N*-alkoxy compound, *e.g. (4)*, is obtained, and with

[7] German Patent 1 112082 (Oct. 21st, 1959), Farbwerke Hoechst AG., inventors: *O. Scherer, G. Hörlein, R. Hühner*, and *G. Schneider*.

[8] *E. Beckmann*, Liebigs Ann. Chem. *365*, 211 (1909).

[9] Swiss Patent 325080 (Dec. 14th, 1957); Inventa AG. für Forschung und Patentverwertung, inventors: *K. Kahr* and *K. Zimmermann*.

[10] *C. Kjellin*, Ber. dtsch. chem. Ges. *26*, 2384 (1893).

[11] *E. Fischer*, Ber. dtsch. chem. Ges. *22*, 1935 (1889); *H. Kall*, Liebigs Ann. Chem. *263*, 264 (1891).

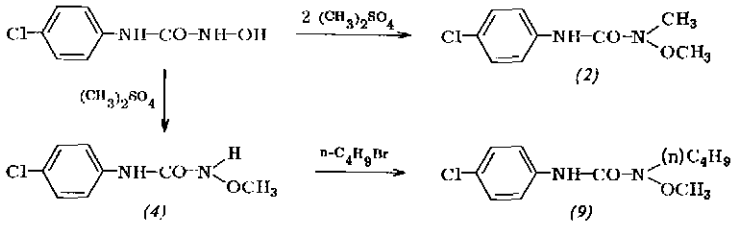
[12] *O. Exner*, Coll. czechoslov. chem. Commun. *26*, 706 (1961).

[13] *Houben-Weyl:* Methoden der organischen Chemie. 4th Edit., Georg Thieme, Stuttgart 1952, Vol. 8, p. 159.

[14] *A. Conduché*, Ann. Chimie (8) *13*, 72 (1908).

[15] German Published Patent Application 1 133360 (Feb. 18th, 1961), BASF; inventors: *G. Steinbrunn*; German Published Patent Application 1 127344 (Feb. 18th, 1960), BASF; inventor: *G. Steinbrunn*.

a second mole of the same or another alkylating agent, the desired *N*-phenyl-*N'*-alkoxy-*N'*-alkylureas, *e.g. (2)* or *(9)*, are produced [16].



The constitution of the products was proved by the identity of their infrared spectra and mixed melting points with those of compounds prepared by method 1.

Unlike the alkoxyureas, the alkylation of *N*-phenyl-*N'*-hydroxyureas must be carried out under very mild conditions because of their sensitivity towards alkali.

Example

N-(3,4-Dichlorophenyl)-*N'*-hydroxyurea (44 g = 0.2 mole) was dissolved in 300 ml of methanol. A mixture of 50 ml of 10 N sodium hydroxide solution and 0.5 mol = 63 g of dimethyl sulfate was then added with efficient stirring at pH 9–10 and a temperature of less than 20 °C, and the reaction mixture was stirred for one hour at room temperature. The product separated as an oil on pouring the mixture into water but solidified after a short time. After filtering and drying, *N*-(3,4-dichlorophenyl)-*N'*-methyl-*N'*-methoxyurea was obtained in 90 % yield. After recrystallization from petroleum ether, the compound had a m.p. of 86–87 °C.

Biological Activity

Of the urea compounds listed in Table 2, *N*-(4-chlorophenyl)-*N'*-methoxy-*N'*-methylurea (Aresin®) and *N*-(3,4-dichlorophenyl)-*N'*-methoxy-*N'*-methylurea (Afalon®) are distinguished by their strong and broad herbicidal activity. However, at the same time, they possess selective properties, *i.e.* they are suited to the management of definite crops, according to their mode of use and the quantities applied.

[16] German Patent 1140925 (Feb. 25th, 1961), Farbwerke Hoechst AG.; inventors: *O. Scherer* and *G. Hörlein*.

Although both compounds show the same spectrum of herbicidal activity (Table 5) they differ in their selective action against cultivated plants. The major field application of Afalon is in the growth of *Umbelliferae*, *e.g.* carrots, celery, caraway, parsnips, parsley, dill, and chervil. Afalon is tolerated by these plants in relatively large quantities both before and after emergence.

Table 5. Herbicidal activity of Aresin and Afalon with 0.3 to 0.5 kg of active material per acre used as pre-emergence treatment.

1. Good to very good activity against:
   camomile varieties, shepherd's purse, orache (*Atriplex*), groundsel, scabious (*Galinsoga parviflora*), dead nettle, charlock, hedge mustard, chickweed, field pennycress, pearlwort [**], speedwell [*], knotgrass varieties [*], and annuel wild oats. [*].
2. Sufficient activity to control:
   hemp-nettle, cleavers, fumitory.
3. Only slight or no control of:
   all perennial root weeds such as thistles, bindweed, dandelion, couch grass, and horsetail.

[*] Only controlled satisfactorily by large amounts of Afalon.

[**] Only controlled satisfactorily by large amounts of Aresin.

Aresin can be used in the culture of broad beans, soya beans, and potatoes. These plants tolerate Aresin well if it is applied between sowing and emergence. Aresin can also be used for weed-killing in the culture of hard and soft fruits and vine immediately prior to emergence and after harvest.

Both Afalon and Aresin are inactivated and destroyed in the soil relatively quickly. The quantities of 0.4–0.8 of active material per acre normally recommended for use in fields and gardens cannot be detected biologically after 3 or 4 months. This is a property of outstanding importance for both market gardening and general crop farming, since as a result of this rapid destruction there is no need to consider possible accumulation of the active material in the soil or danger to the next year's crop.

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Neighboring Group and Substituent Effects in Organosulfur Compounds

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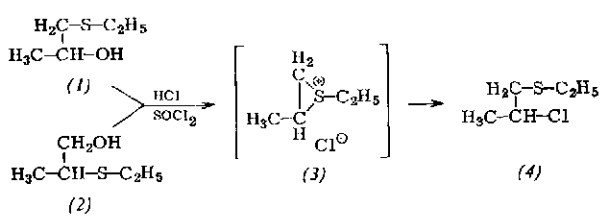
Thioether groups participate in nucleophilic substitution reactions at adjacent carbon atoms, in the addition of alkane and arenesulfenyl halides onto olefinic double bonds, and in elimination reactions which lead to olefins and which proceed via intermediate episulfonium ions. Studies of alkylthioacrylic acid derivatives, which are readily synthetized because of the neighboring group effect, show that the presence of thioether groups in the α-position of acrylic acid systems leads to particularly high reactivity in "head-to-head" dimerizations.

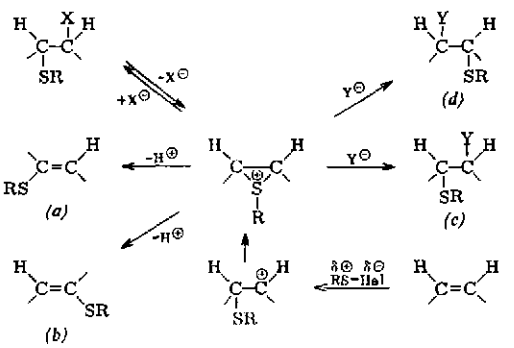
Introduction

The essence of a neighboring group effect may be stated as follows: during a reaction, a grouping adjacent to the reaction center temporarily forms a genuine intramolecular bond to the reaction center. This often results in rearrangements, anomalous acceleration of reactions, and steric effects. A review of this vast subject, which was developed principally by *Winstein* and his school, was published by *Lwowski* in 1958 [1]; the discussion of these problems by *Gould* [2] and *Leffler* [3] should also be mentioned.

Neighboring group effects in organic sulfur compounds were first investigated in the formation and hydrolysis of extremely reactive β-halogenoalkyl thioethers of the "mustard gas" type, $S(CH_2CH_2Cl)_2$ [4-6], where intermediate formation of episulfonium ions was proposed [4,6]. For example, *Fuson* and co-workers [4] obtained the same ethyl β-chloropropyl thioether *(4)* from the two isomeric ethyl β-hydroxypropyl thioethers *(1)* and *(2)*; they explained this by postulating the formation of an intermediate episulfonium salt *(3)*.

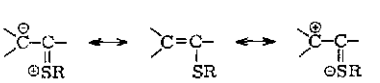


The present review will not restrict itself simply to enumeration of further new preparative examples which involve neighboring group effects of thioether groups in nucleophilic substitution reactions. Provided certain structural prerequisites are satisfied, nucleophilic substitutions are often accompanied by elimination reactions leading to olefins. Thus, it can be expected that neighboring group effects associated with thioethers may also be involved here. Conversely, polar additions of arenesulfenyl halides ArSCl onto olefinic double bonds may be accompanied by intermediate formation of episulfonium ions [7]. The scope of this review has therefore been enlarged to cover all the reactions summarized in Scheme 1.



Scheme 1. Reactions entailing participation of thioether groups. (a), (b): normal and rearranged elimination products; (c), (d): normal and rearranged substitution products.

The possible formation of unsaturated thioether derivatives via neighboring group effects leads to the second aspect of this review, namely substituent effects. In order to form a cyclic sulfonium ion, the thioether group must possess nucleophilic character or a tendency to assume a positively charged state (cf. also Section B). However, in actuality, not only can it donate electrons to the C=C double bond, it can also take up electrons, with the expansion of the octet [8].



Arens et al. [9-11] were the first to use this dualistic nature of sulfur in order to explain the differing effects

[1] *W. Lwowski*, Angew. Chem. *70*, 483 (1958).

[2] *E. S. Gould:* Mechanism and Structure in Organic Chemistry. Holt and Comp., New York 1959, p. 561.

[3] *J.E. Leffler:* The Reactive Intermediates of Organic Chemistry. Interscience Publishers, New York 1956, p. 117.

[4] *R. C. Fuson, C. C. Price,* and *D. M. Burness*, J. org. Chemistry *11*, 475 (1946).

[5] *H. Böhme* and *K. Soll*, Chem. Ber. *81*, 123 (1948).

[6] *P. D. Bartlett* and *C. G. Swain*, J. Amer. chem. Soc. *71*, 1406 (1949).

[7] *N. Kharasch* in: Organic Sulfur Compounds. Pergamon Press, Oxford, New York 1961. Vol. I, p. 375.

[8] *G. Cilento*, Chem. Reviews *60*, 147 (1960).

[9] *J. F. Arens* in *N. Kharasch:* [7], p. 257.

[10] *J. F. Arens* in: Advances in Organic Chemistry, Interscience Publishers, New York 1960, Vol. 2, p. 152.

[11] *H. C. Volger* and *J. F. Arens*, Recueil Trav. chim. Pays-Bas *77*, 1170 (1958).

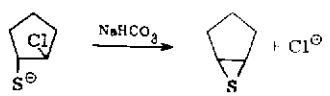
they observed in the addition reactions of vinyl and acetylenic ethers on one hand and of the corresponding thioethers on the other.

We shall first discuss briefly the rapidly developing chemistry of episulfides [12–14]; during their formation, the mercaptide anion acts directly, or more frequently indirectly, as a neighboring group.

A. Neighboring Group Effects

1. The Mercaptide Anion as Neighboring Group

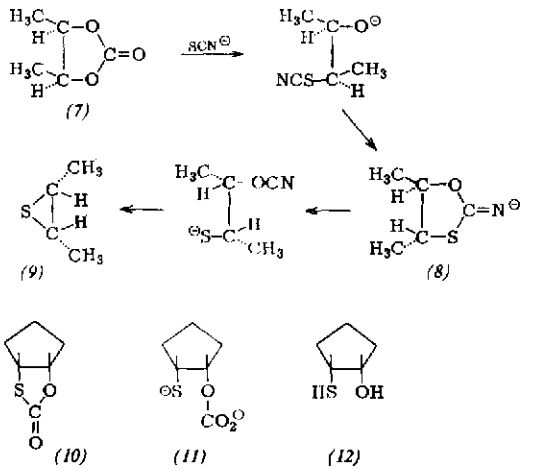
The mercaptide group participates [18] in the mild alkaline hydrolysis of β-chloroethanethiol [15], *trans*-1-chloro-2-mercaptocyclopentane *(5)* [16], *O*-acetylmercaptoethanol [17], and *trans*-1-acetoxy-2-mercaptocyclohexane [17] which leads smoothly to the corresponding episulfides, *e.g. (6)*.



(5) *(6)*

In the processes most commonly used today for the preparation of episulfides, *e.g.* from epoxides and thiocyanates [16], from thiourea [19], from carbon oxysulfide [20], from cyclic carbonates and thiocyanates [21], and from *O,S*-ethylene thiocarbonate [22], the mercaptide anion acts essentially as a neighboring group, since in all of these reactions, intermediates of type *(8)* are either the starting materials or participate at some stage of the reaction. The existence of such intermediates was postulated by *van Tamelen* [16] as early as 1951 to account for the reaction between epoxides and potassium thiocyanate. The formulae describing the preparation of *cis*-2,3-butylene sulfide *(9)* from *meso*-2,3-butylene carbonate *(7)* [21] also indicate the steric course of the reaction.

However, if a cyclic thiocarbonate grouping is attached to a cyclopentane ring as in *(10)*, cleavage with base does not yield an episulfide, but rather the *cis*-1,2-mono-



(7) *(8)* *(9)*

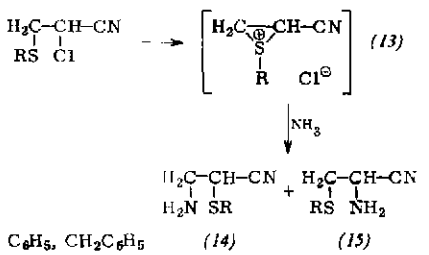
(10) *(11)* *(12)*

thioglycol *(12)* [23]: the β-mercaptoalkyl carbonate grouping *(11)* which occurs in one intermediate is incapable of free rotation and thus cannot assume the conformation required for *trans*-episulfide ring closure. No such restrictions exist, of course, in the cleavage of open-chain thiolcarbonates.

2. The Alkylthio Residue as Neighboring Group

a) *Nucleophilic Substitutions*

The reactions of α-chloro-β-alkyl- or α-chloro-β-arylthiopropionitriles and the corresponding esters (readily obtainable via base-catalysed addition of thiols or thiophenols onto α-chloroacrylonitrile and α-chloroacrylic esters) with ammonia, potassium phthalimide, or sodium saccharin proceed predominantly with migration of the thioether group to the α-position *(14)* [24–27].



(13) *(14)* *(15)*

R = C_2H_5, C_6H_5, $CH_2C_6H_5$

In these reactions, one of the factors determining the point of cleavage of the episulfonium ring *(13)* is evidently nucleophilicity of the attacking agent. Reaction with liquid ammonia produces only traces of the normal substitution product *(15)*; with the much less nucleophilic saccharin anion in dimethylformamide, the products are an α-benzosulfimido derivative of type *(15)* and its β-isomer *(14)*. The ratio of the two products is 1:3, but the overall yield is much lower [25].

[12] *A. Schönberg* in *Houben-Weyl:* Methoden der organischen Chemie. Thieme, Stuttgart 1955, Vol. IX, p. 149.

[13] *E. E. Reid:* Organic Chemistry of Bivalent Sulfur. Chemical Publishing Co., New York 1960, Vol. III, p. 14.

[14] *L. N. Owen* in *N. Kharasch:* [7], p. 199.

[15] *W. Coltof*, U.S. Pat. 2183860, (Dec. 19th, 1940); Chem. Abstr. *34*, 2395 (1940).

[16] *E. E. van Tamelen*, J. Amer. chem. Soc. *73*, 3444 (1951).

[17] *L. W. C. Miles* and *L. N. Owen*, J. chem. Soc. (London) *1952*, 817.

[18] *J. S. Harding* and *L. N. Owen*, J. chem. Soc. (London) *1954*, 1528.

[19] *F. G. Bordwell* and *H. M. Anderson*, J. Amer. chem. Soc. *75*, 4959 (1953).

[20] *J. A. Durden, H. A. Stansbury*, and *W. H. Catlette*, J. org. Chemistry *26*, 836 (1961).

[21] *S. Searles, H. R. Hays*, and *E. F. Lutz*, J. org. Chemistry *27*, 2832 (1962).

[22] *D. D. Reynolds, D. L. Fields*, and *D. L. Johnson*, J. org. Chemistry *26*, 5130 (1961).

[23] *E. J. Reist, J. H. Osiecki, A. Benitez, L. Goodman*, and *B. R. Baker*, J. org. Chemistry *26*, 3554 (1961).

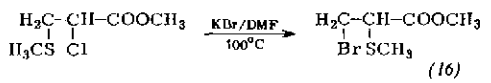
[24] *K.-D. Gundermann* and *F. Micheel*, Liebigs Ann. Chem. *578*, 45 (1952).

[25] *K.-D. Gundermann*, Liebigs Ann. Chem. *588*, 167 (1954).

[26] *K.-D. Gundermann* and *R. Thomas*, Chem. Ber. *89*, 1263 (1956).

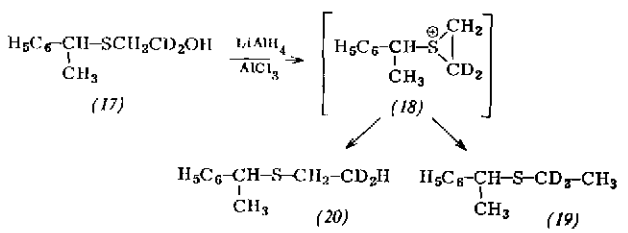
[27] *K.-D. Gundermann* and *R. Thomas*, Chem. Ber. *91*, 1330 (1958).

Transhalogenation of α - chloro - β - alkylthiopropionic esters with potassium bromide in dimethylformamide (DMF) yields the rearrangement product *(16)*, as well as other products (see below) which are also formed via an episulfonium salt of type *(13)* [27].



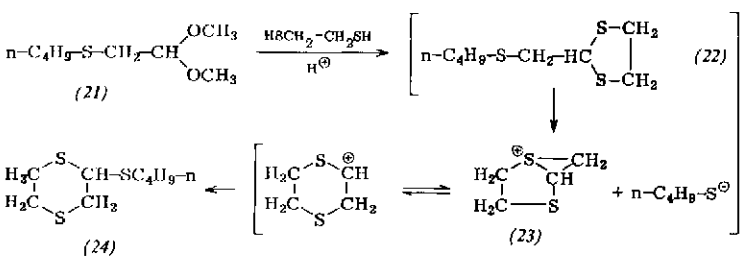
(16)

The reduction of the deuterated β-hydroxyethyl thioether *(17)* with lithium aluminum hydride and aluminum chloride leads to a mixture of approximately equal amounts of the thioethers *(19)* and *(20)*; thus the episulfonium ion *(18)* is cleaved symmetrically under these reaction conditions [28].



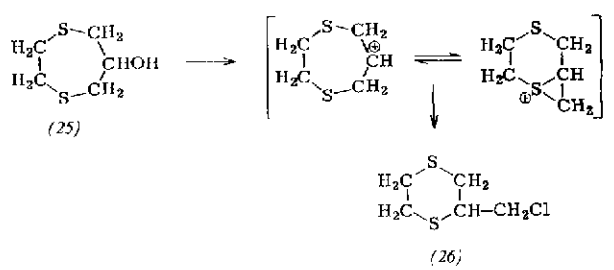
(17) *(18)* *(20)* *(19)*

In an attempt to prepare the dithiolane *(22)* from n-butylthioacetaldehyde dimethylacetal *(21)*, the product actually obtained was 2-butylthio-1,4-dithiane *(24)* [29]; this ring expansion may be explained by the intermediate formation of the episulfonium mercaptide *(23)*.



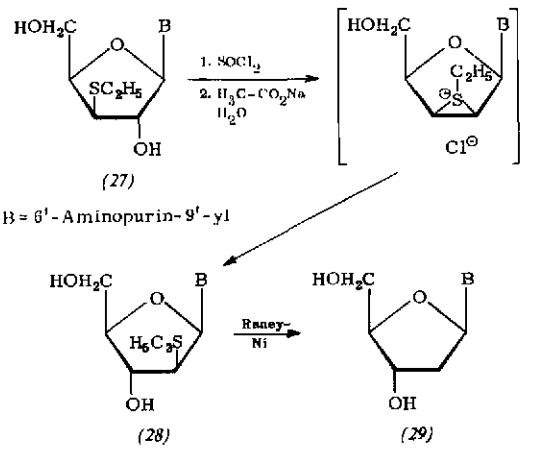
(21) *(22)* *(24)* *(23)*

The reaction of 3,6-dithia-1-cycloheptanol *(25)* to give 2-chloromethyl-1,4-dithiane *(26)*, which proceeds with ring contraction, had already been reported some time ago [30].



(25) *(26)*

The first example of intentional utilization of the neighboring group effect of a thioether group was the isomerization of the 3-deoxy-3-ethylthioxylose derivative *(27)* to the 2-deoxy-2-ethylthioarabinose derivative *(28)*. This isomerization was a step in the first synthesis of a naturally occurring purine-2'-deoxynucleoside, *viz.* 2'-deoxyadenosine *(29)* [31].



(27)

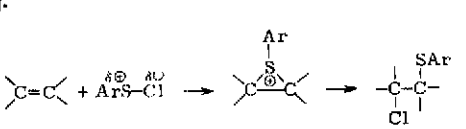
B = 6'-Aminopurin-9'-yl

(28) *(29)*

Episulfonium salts are evidently also involved in the Friedel-Crafts reactions of β-halogenoalkyl thioethers [32]. For new studies of β-hydroxyethyl β-chloroethyl sulfide, see [33, 34].

b) *Addition of Alkane- and Arenesulfenyl Chlorides onto C=C Double Bonds*

The studies of *Kharasch* et al. [35] showed that additions of arenesulfenyl chlorides ArSCl very frequently proceed via a polar mechanism involving an episulfonium intermediate [36].



This mechanism is confirmed *inter alia* by the effect of the polarity of the solvent [37]. Thus, for example, the addition of 2,4-dinitrobenzenesulfenyl chloride onto cyclohexene proceeds 3000 times faster in acetic acid than in carbon tetrachloride. Another confirmation of the

[28] *E. L. Eliel, L. A. Pilato,* and *V. G. Badding,* J. Amer. chem. Soc. *84,* 2377 (1962).

[29] *H. J. Schneider* and *J. J. Bagnell,* J. org. Chemistry *26,* 3009 (1961).

[30] *R. C. Fuson* and *A. J. Speziale,* J. Amer. chem. Soc. *71,* 1582 (1949).

[31] *C. D. Anderson, L. Goodman,* and *B. R. Baker,* J. Amer. chem. Soc. *81,* 3967 (1959).

[32] *D. Klamann* and *H. Bertsch,* Chem. Ber. *88,* 1226 (1955).

[33] *K. C. Tsou, H. F. Su, C. Segebarth,* and *U. Mirarchi,* J. org. Chemistry *26,* 4987 (1961).

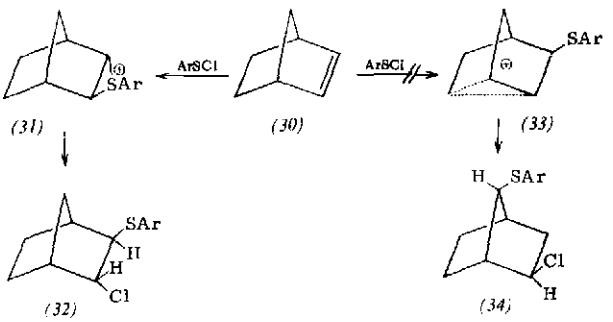
[34] *D. Welti* and *D. Whittaker,* J. chem. Soc. (London) *1962,* 3955.

[35] *N. Kharasch* in: [7], p. 375.

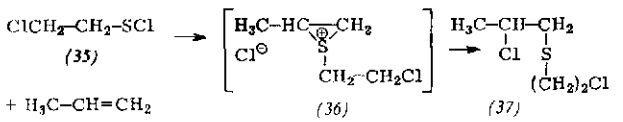
[36] *N. Kharasch* and *M. Buess,* J. Amer. chem. Soc. *71,* 2724 (1949).

[37] *D. R. Hogg* and *N. Kharasch,* J. Amer. chem. Soc. *78,* 2728 (1956).

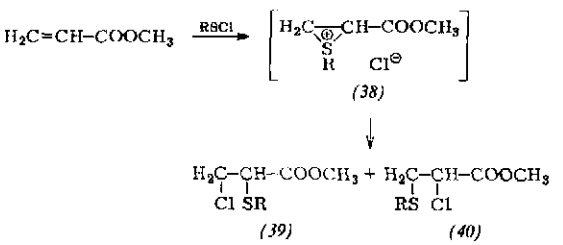
mechanism is obtained from the stereospecificity of the reaction: thus, the *trans*-addition expected with an episulfonium intermediate has been demonstrated with several pairs of olefinic geometric isomers [38–40]. *trans*-Addition has also been observed with bicyclic olefins such as norbornene *(30)*. From this it may be concluded that the reaction proceeding via the episulfonium ion *(31)* to form *(32)* is energetically favored over that proceeding via a feasible [1] nortricyclene cation intermediate *(33)* [41–43] to give *(34)*.



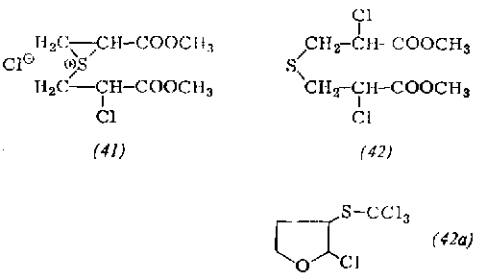
Some time ago, *Fuson* et al. [4] already postulated that the reaction of propylene with β-chloroethanesulfenyl chloride *(35)* to give *(37)*, which is the product predicted by the Markovnikoff rule, proceeds via the episulfonium ion *(36)*.



Addition of alkanesulfenyl chlorides onto acrylic acid derivatives affords not only α-chloro-β-alkylthiopropionic acid derivatives *(40)* [44], but also α-alkylthio-β-chloropropionic acid derivatives *(39)* [45].



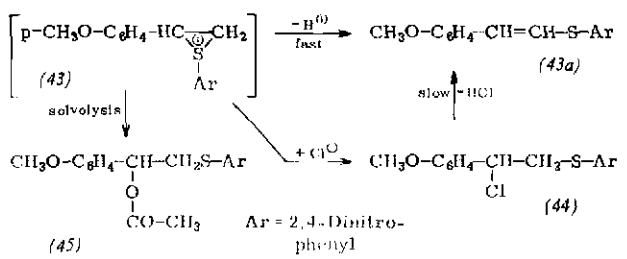
The latter would be expected as exclusive products if no intermediate *(38)* were to occur and if the polarities of the acrylic acid derivative and of the alkanesulfenyl chloride were the sole factors determining the direction of the addition [46]. Methanesulfenyl chloride and methyl acrylate, for example, react in ether to form the isomers *(39)* and *(40)* (R = CH_3) in a ratio of approximately 1:1; the presence of α-chloro-β-methylthiopropionic ester in the addition product was demonstrated by its conversion into β-methanesulfonylpropionic acid. Here oxidation to the sulfone must take place before reductive replacement of the chlorine atom in order to prevent rearrangement (see Section A.2.a). This also applies to the very smooth reaction of sulfur dichloride and methyl acrylate, which gives rise to a mixture of isomeric dimethyl dichlorothiapimelates; the product contains about 30% dimethyl 2,6-dichloro-4-thiapimelate *(42)*, formed via the episulfonium ion *(41)* [47,48].



Trihalogenomethanesulfenyl chlorides, such as Cl_3C–SCl and F_3C–SCl, add onto olefinic double bonds. Normally, this is a radical reaction [48a,b]. Recently, however, *Senning* and *Lawesson* [48c] observed polar addition of Cl_3C–SCl onto 2,3-dihydrofuran, which led to *(42a)*, the product expected according to Markovnikoff's rule.

c) β-*Eliminations*

The reaction of 2,4-dinitrobenzenesulfenyl chloride with *p*-methoxystyrene in glacial acetic acid gives the addition product *(44)*, the solvolysis product *(45)*, and also the product of HCl elimination *(43a)*. The latter is evidently formed directly by cleavage of a proton from the episulfonium ion *(43)*. It is not formed in a secondary reaction from *(44)*, since the rate of HCl cleavage from *(44)* under analogous conditions is much lower than the rate of formation of *(43a)* during the addition reaction [49].



[38] *D. J. Cram*, J. Amer. chem. Soc. *71*, 3883 (1949).

[39] *N. Kharasch* and *A. J. Havlik*, J. Amer. chem. Soc. *75*, 3734 (1953).

[40] *A. J. Havlik* and *N. Kharasch*, J. Amer. chem. Soc. *77*, 1150 (1955).

[41] *S. J. Cristol, R. P. Arganbright, G. D. Brindell*, and *R. M. Heitz*, J. Amer. chem. Soc. *79*, 6035 (1957).

[42] *H. Kwart* and *R. K. Miller*, J. Amer. chem. Soc. *78*, 5678 (1956).

[43] *H. Kwart* and *L. J. Miller*, J. Amer. chem. Soc. *83*, 4552 (1961).

[44] *H. Brintzinger* and *M. Langheck*, Chem. Ber. *87*, 325 (1954).

[45] *K.-D. Gundermann* and *R. Huchting*, Chem. Ber. *95*, 2191 (1962).

[46] *I. L. Knunyants, N. D. Kuleshova* and *M. G. Linkova*, Dokl. Akad. Nauk SSSR *135*, 81 (1960).

[47] *K.-D. Gundermann* and *C. Burba*, Chem. Ber. *94*, 2157 (1961).

[48] *K.-D. Gundermann* and *R. Huchting*, unpublished results.

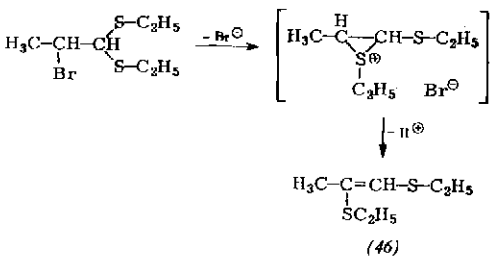
[48a] *V. Prey, E. Gutschik*, and *H. Berbalk*, Mh. Chem. *91*, 794 (1960).

[48b] *J. F. Harris*, J. Amer. chem. Soc. *84*, 3148 (1962).

[48c] *A. Senning* and *S. O. Lawesson*, Tetrahedron *19*, 695 (1963).

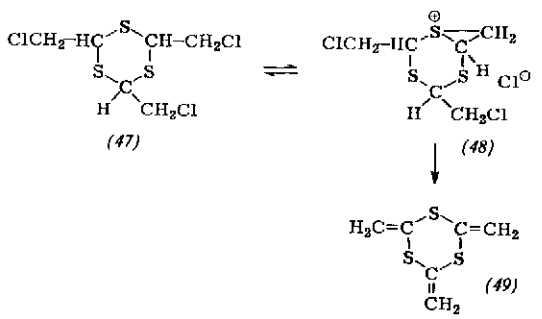
[49] *W. L. Orr* and *N. Kharasch*, J. Amer. chem. Soc. *78*, 1201 (1956).

Open-chain α-halogenomercaptals undergo spontaneous loss of hydrogen halide to form α,β-bis(alkylthio)olefins *(46)* [50–52].



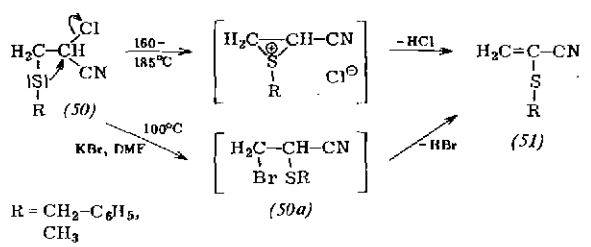
(46)

In contrast to this E_1 reaction, which involves migration of a thioether group, 2,4,6-tri(chloromethyl)-1,3,5-trithiane *(47)* with bases splits off HCl in a normal E_2 elimination, forming *(49)* [53]. Episulfonium structures such as *(48)* have been postulated as intermediates of this reaction [53] (cf. the conversion of *(25)* into *(26)* in Section A 2a).



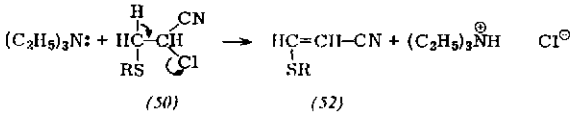
(47) *(48)* *(49)*

On heating to 165–180 °C, α-chloro-β-alkylthiopropionitriles *(50)* are converted into α-alkylthioacrylonitriles *(51)*.



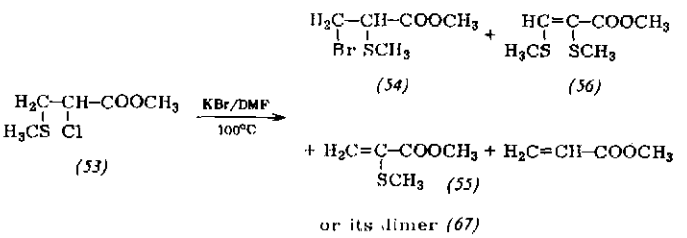
(50) *(50a)* *(51)*

The latter are easier to obtain by treating *(50)* with potassium bromide in dimethylformamide at 100 °C [26,54]. In the absence of KBr, but under otherwise identical conditions, the quantity of hydrogen halide formed (corresponding to the yield of α-alkylthioacrylonitrile *(51)* [23]) is only one-third of that produced in the presence of KBr; therefore the unstable α-alkylthio-β-bromonitrile *(50a)* probably occurs as intermediate. Under conditions which favor an E_2 mechanism [55], *e.g.* in benzene with triethylamine as proton acceptor, compounds of type *(50)* give β-alkylthioacrylonitriles *(52)* in over 80 % yield. The latter may also be obtained directly from α-chloroacrylonitrile, thiols, and triethylamine [25,54,56]. Evidently, the HCl is split off from the chloronitrile *(50)* without participation of the thioether group. Kinetic measurements [57] show that the liberation of chloride ions is a second-order reaction.



(50) *(52)*

The removal of hydrogen chloride from α-chloro-β-alkylthiopropionic esters proceeds in more complex fashion: the methyl ester *(53)* yields methyl α-methylthio-β-bromopropionate *(54)*, methyl α-methylthioacrylate *(55)* or its dimer *(67)* (cf. Section B 1a), methyl α,β-bis(methylthio)acrylate *(56)*, and methyl acrylate [27].

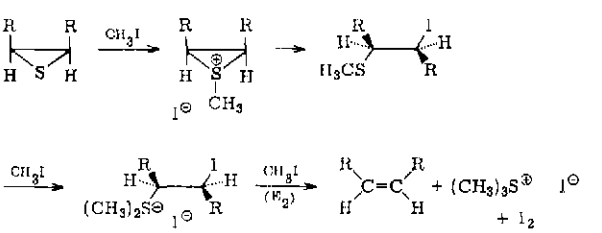


(53) *(54)* *(56)* *(55)* or its dimer *(67)*

If the reaction temperature is raised to 120–130 °C, *(56)* becomes the predominant product. If, however, the reaction is carried out at 100 °C in the presence of triethylamine, *(55)* is formed in 77 % yield. Other α-alkylthioacrylic esters have also been prepared in this way [27].

Unlike the nitriles *(50)*, esters of type *(53)* yield α- as well as β-alkylthioacrylic esters even under conditions which generally lead to E_2 reactions [57]. β-Alkylthioacrylic esters may also be obtained from β-alkoxyacrylic esters [58] or from propiolic esters [59,60].

Investigation of the olefinic hydrocarbons formed by desulfurization of episulfides with methyl iodide [61,62] showed that this reaction proceeds very stereospecifically [63]. This fact may be explained by the following mechanism [63,64]:



[50] *E. Rothstein*, J. chem. Soc. (London) *1940*, 1553.

[51] *E. Rothstein* and *R. Whiteley*, J. chem. Soc. (London) *1953*, 4012.

[52] *W. E. Parham, J. Heberling*, and *H. Wynberg*, J. Amer. chem. Soc. *77*, 1169 (1955).

[53] *A. S. Matlack, J. C. W. Chien*, and *D. S. Breslow*, J. org. Chemistry *26*, 1455 (1961).

[54] *K.-D. Gundermann*, Chem. Ber. *88*, 1432 (1955).

[55] *J. F. Bunnett*, Angew. Chem. *74*, 731 (1962); Angew. Chem. internat. Edit. *1*, 225 (1962).

[56] *K.-D. Gundermann* and *R. Thomas*, unpublished results.

[57] *G. Pape*, Ph.D. Thesis, Universität Münster, 1961.

[58] *W. J. Croxall, J. O. van Hook*, and *R. Luckenbaugh*, J. Amer. chem. Soc. *71*, 2736 (1949).

[59] *W. E. Truce* et al., J. Amer. chem. Soc. *82*, 3799 (1960).

[60] *F. Montanari*, Tetrahedron Letters *1960*, No. 4, 18.

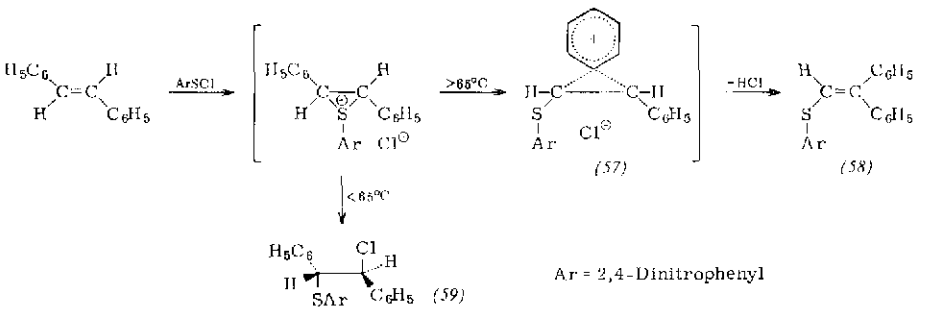
[61] *M. Delepine* and *P. Jaffeux*, C. R. hebd. Séances Acad. Sci. *172*, 158 (1921).

[62] *C. C. J. Culvenor, W. Davies*, and *N. S. Heath*, J. chem. Soc. (London) *1949*, 282.

[63] *G. K. Helmkamp* and *D. J. Pettit*, J. org. Chemistry *25*, 1754 (1960).

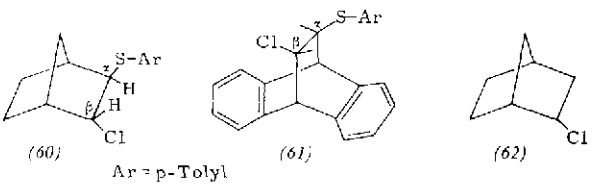
[64] *G. K. Helmkamp* and *D. J. Pettit*, J. org. Chemistry *27*, 2942 (1962).

The relative magnitudes of the neighboring group effects of the thioether groups (with episulfonium ions as intermediates) and of aryl groups (with phenonium ions *(57)* as intermediates [1]) may be gleaned from the following fact: in boiling glacial acetic acid, the reaction of *trans*-stilbene with 2,4-dinitrobenzenesulfenyl chloride proceeds with phenyl migration to form *(58)*, while up to 65 °C normal *trans*-addition to give *(59)* occurs [65,66].



d) *Steric Peculiarities; on the Existence of Stable Episulfonium Compounds*

The *trans*-α-arylthio-β-chloro derivatives *(60)* and *(61)* are solvolyzed only very slowly, the rate being about the same as that of norbornyl chloride *(62)*. The absence of a thioether neighboring group effect may be accounted for by assuming that not only the *trans*-orientation [1,67] but also a coplanar arrangement of the four atoms S, C(α), C(β), and Cl is required for the formation of an episulfonium ring. However, this coplanarity is prevented by the rigidity of the ring systems in *(60)* and *(61)* [68].



Well defined, stable episulfonium salts have not yet been prepared [62]. This is in contrast to ethylene-imonium salts which play a quite analogous role in the neighboring group effect of $-NR_2$ groups to that of an $-SR$ group [69].

B. Substituent Effects

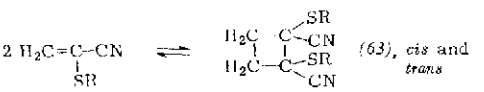
The dualistic nature of the thioether sulfur, which can act both as an electron donor and an acceptor [8–11,70] is the reason for its special behavior as a neighboring group in mesomeric systems. The same dualistic nature governs the unique behavior of the thioether group as a substituent on α-carbon cationic [71–73] and anionic intermediates.

This distinguishes thioether groups not only from sulfinyl and sulfonyl [74,75] but also from the alkoxy and the dialkylamino groups, which follow the octet principle.

1. Thioether Groups as Substituents in Acrylic Acid Derivatives

a) *α-Alkylthioacrylic Acid Derivatives*

α-Alkylthioacrylonitriles [26,54] undergo the same base-catalysed addition reactions as acrylonitrile itself [76] with thiols, ammonia, and CH-acidic compounds such as malonic and acetoacetic esters [77]. However, the most remarkable characteristic of α-alkylthioacrylonitriles, which had never been observed with any simple acrylonitrile derivative, is their ability to dimerize spontaneously, even at room temperature, to form 1,2-bis(alkylthio)cyclobutane-1,2-dicarbonitriles *(63)*, which frequently crystallize well [78].



This dimerization is a temperature- and structure-dependent equilibrium reaction and is influenced neither by radical formers such as azobisisobutyronitrile nor by radical scavengers such as hydroquinone and pyrogallol [79]. Even at 100 °C, at least 50 % of *(63)* is decomposed to the monomer. Despite its thermal instability, *(63)* can be saponified smoothly with 20 % aqueous-alcoholic

[65] *N. R. Slobodkin* and *N. Kharasch*, J. org. Chmistry *25*, 866 (1960).

[66] *N. R. Slobodkin* and *N. Kharasch*, J. Amer. chem. Soc. *82*, 5837 (1960).

[67] *H. L. Goering* and *K. L. Howe*, J. Amer. chem. Soc. *79*, 6542 (1957).

[68] *S. J. Cristol* and *R. P. Arganbright*, J. Amer. chem. Soc. *79*, 3441 (1957).

[69] *N. J. Leonard* and *K. Jann*, J. Amer. chem. Soc. *84*, 4806 (1962).

[70] *W. A. Sheppard*, J. Amer. chem. Soc. *83*, 4860 (1961).

[71] *H. Bredereck*, *R. Gompper*, *H. Herlinger*, and *E. Woitun*, Chem. Ber. *93*, 2423 (1960).

[72] *G. Kresze*, *W. Schramm*, and *G. Cleve*, Chem. Ber. *94*, 2060 (1961).

[73] *W. E. Parham*, *M. A. Kalnins*, and *D. R. Theissen*, J. org. Chemistry *27*, 2698 (1962).

[74] *H. H. Szmant* in *N. Kharasch:* [7], p. 154.

[75] *J. Stratting* in *N. Kharasch:* [7], p. 146.

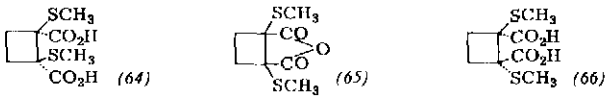
[76] *H. A. Bruson* in: Organic Reactions. Wiley New York 1952, Vol. V, p. 79.

[77] *K.-D. Gundermann*, Chem. Ber. *90*, 72 (1957).

[78] *R. Huchting*, Ph.D. Thesis, Universität Münster, 1960.

[79] *K. D. Gundermann* and *R. Huchting*, Chem. Ber. *92*, 415 (1959).

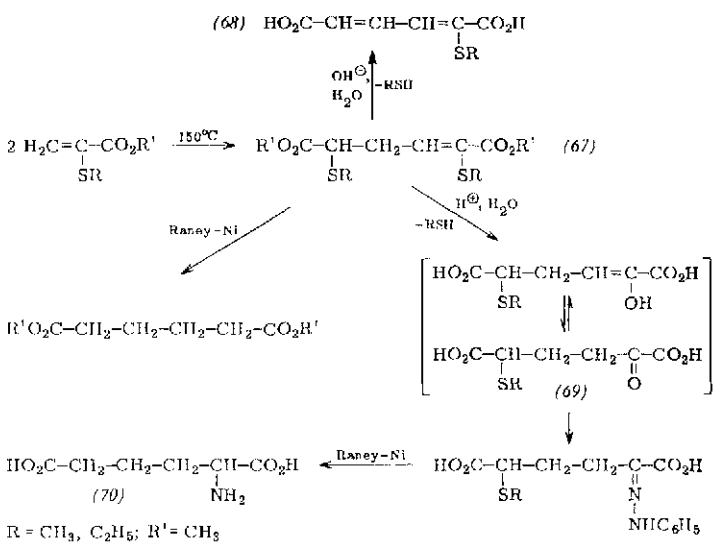
alkali to mixtures of the corresponding *cis*- and *trans*-dicarboxylic acids. The structures of the latter were demonstrated by reductive desulfurization with Raney nickel to give 1,2-cyclobutanedicarboxylic acid. In the case of the methylthio derivatives, the configuration of the *cis*-form *(64)* was established by its conversion into the anhydride *(65)*. That of the *trans*-derivative was proved by its separation into the expected optical antipodes, the dextrorotatory form of which was isolated [80].



(64) *(65)* *(66)*

The dimerization of the α-alkylthioacrylonitriles is evidently not stereospecific [78,80]. On heating dimeric α-methylthioacrylonitrile with azobisisobutyronitrile for several days at 75 °C, dark, glassy polymers are obtained [81].

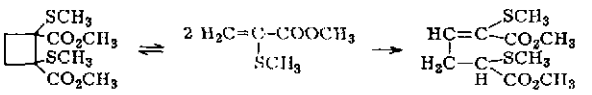
In the case of the α-alkylthioacrylic esters [27,82], polymerization to clear, elastic resins takes place instead of spontaneous cyclodimerization. At room temperature, this reaction is complete within a few days and is not prevented by inhibitors such as hydroquinone, phenothiazine, or t-butylcatechol. However, on heating at 100–150 °C, the esters also dimerize both in dimethylformamide and in the absence of solvent, but do not form cyclobutane derivatives; instead they yield the α,α′-bis(alkylthio)-α,β-dihydromuconic esters *(67)*, the structures of which were proved by reductive desulfurization to give adipic esters, by alkaline hydrolysis to α-alkylthiomuconic acids *(68)*, and by acidic hydrolysis to α-keto-α′-alkylthioadipic acids *(69)*, which are then converted into α-aminoadipic acid *(70)* [83].



(68) *(67)* *(69)* *(70)*

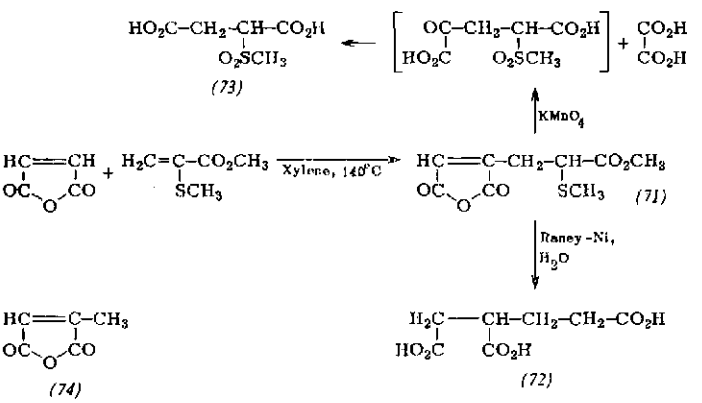
R = CH_3, C_2H_5; R′ = CH_3

Infrared and ultraviolet spectroscopy also confirm the dihydromuconic ester structure [84]. The dihydromuconic ester *(67a)* is also formed at 150 °C from the cyclobutanedicarboxylic esters *(67b)*, which are prepared via the acids *(64)* and *(65)* [80].



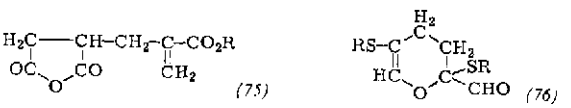
(67b), *cis* and *trans* *(67a)*

With maleic anhydride in boiling xylene, methyl α-methylthioacrylate gives the substituted maleic anhydride *(71)* [*]. Proof of structure *(71)* is provided by reductive desulfurization, by its hydrolysis to β-carboxy-



(73) *(71)* *(74)* *(72)*

adipic acid *(72)*, and by oxidative degradation with $KMnO_4$ to oxalic acid and methanesulfonylsuccinic acid *(73)*. Moreover, its infrared spectrum shows that the C=O bands of the anhydride and the C=C band are located in the same positions as those in citraconic anhydride *(74)* [85]. Any other known reactions of unsaturated esters with maleic anhydride always lead to substituted succinic anhydrides in type of "ene" synthesis [86]; *e.g.* methacrylic ester and maleic anhydride give compound *(75)* [87].



(75) *(76)*

R = CH_3, C_2H_5, C_6H_5–CH_2

A strong tendency to dimerize is also shown by the α-alkylthioacroleins. Attempts to prepare these by analogy to the preparation of the esters *(55)* by elimination of HCl from the very unstable addition products of acrolein

[80] *K.-D. Gundermann* and *R. Huchting*, Chem. Ber. *95*, 632 (1962).

[81] *R. Thomas*, Ph.D. Thesis, Universität Münster, 1958.

[82] *K.-D. Gundermann* and *H. Schulze*, Chem. Ber. *94*, 3254 (1961).

[83] *K.-D. Gundermann* and *R. Thomas*, Chem. Ber. *92*, 1503 (1959).

[84] *K.-D. Gundermann* et al.: Forschungsberichte des Landes Nordrhein-Westfalen. Westdeutscher Verlag, Köln and Opladen 1963, No. 1219, p. 16.

[*] For the mechanism of formation of *(71)*, see Section B. 2 and [82].

[85] *K.-D. Gundermann*, unpublished data.

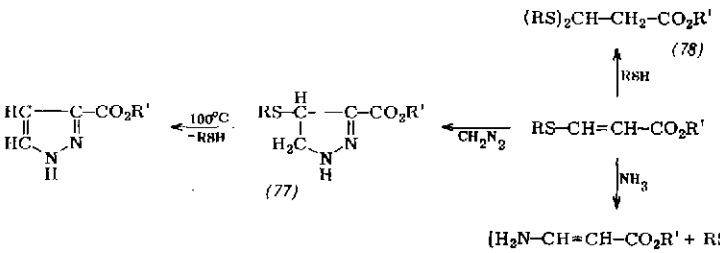
[86] See *K. Alder* and *H. v. Brachel*, Liebigs Ann. Chem. *651*, 141 (1962), who give further references to "ene" syntheses.

[87] *M. Lora-Tamayo*, *F. Martín-Panizo*, and *F. Bonnet*, An. Real. Soc. espan. Fisica. Quim., Ser. B., *51*, 711 (1955); Chem. Abstr. *50*, 11 246e (1956).

and alkanesulfenyl chlorides led only to the dimers *(76)*, which, like the dimer of acrolein itself [88], are products of a diene synthesis [85,89]. The only free α-alkylthioacrylic acid known so far is the crystalline α-cyclohexylthioacrylic acid obtained from cyclohexanesulfinylsuccinic acid. It decomposes slowly even in the solid state, and in acidic solution is rapidly hydrolysed to cyclohexanethiol and pyruvic acid [90].

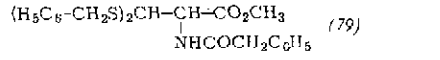
b) *β-Alkylthioacrylic Acid Derivatives and Related Compounds* [91]

β-Alkylthioacrylic acid derivatives are distinctly more stable than their highly reactive α-isomers and tend neither to cyclodimerize spontaneously nor to polymerize. Nevertheless, their C=C double bond reacts with nucleophilic reagents. Thus, methyl β-methylthioacrylate and diazomethane react smoothly to yield the ester *(77)*, which loses methanethiol on heating above 100 °C to

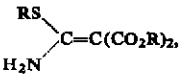


form methyl pyrazole-3-carboxylate [57]. (The unstable pyrazolinecarboxylic esters, which are obtained from α-alkylthioacrylic esters and diazomethane, lose thiol even at room temperature and produce pyrazole derivatives; nitrogen cleavage starts at 50 °C resulting in 1-alkylthiocyclopropane-1-carboxylic ester, among other products [92]). Bases catalyse the addition of thiols onto β-alkylthioacrylic esters and nitriles to yield β,β-bis(alkylthio)propionic esters *(78)* or nitriles [57].

The latter are also obtained by the reaction of β-alkylthioacrylic acid derivatives with liquid ammonia; here, the thioether groups are probably partially replaced by amino groups in a nucleophilic substitution; the thiol released then adds onto unconverted starting material. *Knunyants* et al. [93] synthetized thioacetals of penaldic esters *(79)* in this way by addition of thiols onto α-acylamino-β-alkylthioacrylic esters in liquid ammonia.



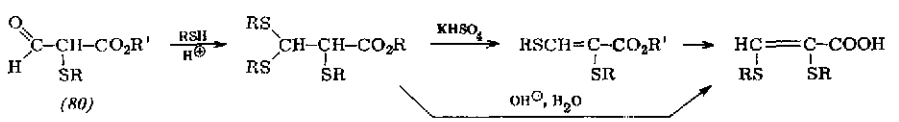
The ease with which β-thioether groups of compounds of the acrylic acid type are replaced by nucleophiles such as ammonia, hydrazine, and their derivatives or by CH-acidic substances has frequently been noted in the past. Thus, ethylthiomethylenemalonic ester $C_2H_5S-CH=C(CO_2C_2H_5)_2$ reacts with ammonia to afford aminomethylenemalonic ester, $H_2N-CH=C(CO_2C_2H_5)_2$ [94]. The thioether groups of ketene mercaptal derivatives of the type $(RS)_2C=C(CO_2R)_2$ can be replaced successively with amino groups to yield ketene-*N,S*-acetals,



and ketene aminals, $(H_2N)_2-CH=C(CO_2R)_2$ [95]. *Truce* [96] has reviewed the literature up to 1960 on free β-alkyl- and β-arylthioacrylic acids which are of interest for the elucidation of the mechanism of nucleophilic and radical addition of thiols and thiophenols onto acetylene derivatives.

c) *α,β-Bis(alkylthio)acrylic Acid Derivatives*

In addition to their preparation by transhalogenation of α-chloro-β-alkylthiopropionic esters [27] (Section A.2.c) or by radical addition of thiols onto alkylthiopropionic esters [97], α,β-bis(alkylthio)acrylic esters can generally be produced from formylalkylthioacetic esters *(80)* [98–100].



As in the case of transhalogenation [27], here the principal products are the *trans*-forms, *e.g. (83)*, in which the two alkylthio groups are *cis* to each other. The configuration of *(83)* is indicated by the fact that the same uniformly crystalline α,β-bis(benzylthio)acrylic acid *(81)* is obtained by each of the two paths and can be converted very smoothly both into the 1,4-dithiacyclohex-2-ene-2-carboxylic acid *(84)* and into the higher-melting α,β-bis(methylthio)acrylic acid *(83)* [100].

[88] *K. Alder* and *E. Rüden*, Ber. dtsch. chem. Ges. *74*, 920 (1941).

[89] *K. Müller*, Diploma Thesis, Universität Münster, 1960.

[90] *B. Weibull*, Ark. Kem. *3*, 225 (1951).

[91] *E. E. Reid*, [13], p. 181.

[92] *K.-D. Gundermann* and *R. Thomas*, Chem. Ber. *93*, 883 (1960).

[93] *O. V. Kildisheva, M. G. Linkova, S. S. Tayz*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1957*, 849.

[94] *K.-D. Gundermann*, Liebigs Ann. Chem. *578*, 48 (1952).

[95] *R. Gompper* and *W. Toepfl*, Chem. Ber. *95*, 2871, 2881 (1962); here further references to older literature are given.

[96] *W. E. Truce* in *N. Kharasch*: [7], p. 112.

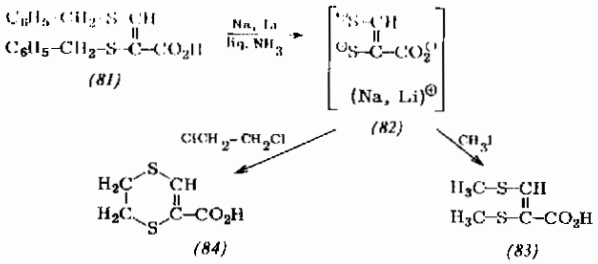
[97] *J. Bonnema* and *J. F. Arens*, Recueil Trav. chim Pays-Bas *79*, 1137 (1960).

[98] *T. B. Johnson* and *H. H. Guest*, Amer. chem. J. *42*, 271 (1909).

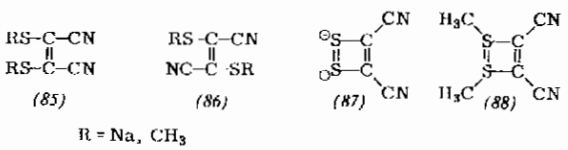
[99] *J. Bonnema, H. J. Alkema*, and *J. F. Arens*, Recueil Trav. chim. Pays-Bas *79*, 937 (1960).

[100] *K.-D. Gundermann* and *G. Pape*, Chem. Ber. *95*, 2076 (1962).

Debenzylation of *(81)* yields a relatively large amount (up to 47 %) of bibenzyl; this also points to a *cis*-relationship of the benzylthio groups in *(81)*.



Simmons et al. [102] also found this preferential formation and configurational stability of systems with *cis*-mercapto and alkylthio groups in the 1,2-dimercaptomaleo- and -fumarodinitriles and their *S*-alkyl derivatives *(85)* and *(86)*, which were discovered by *Bähr* and *Schleitzer* [101], and discussed the possibility that resonance structures such as *(87)* or *(88)* may be the cause of this.



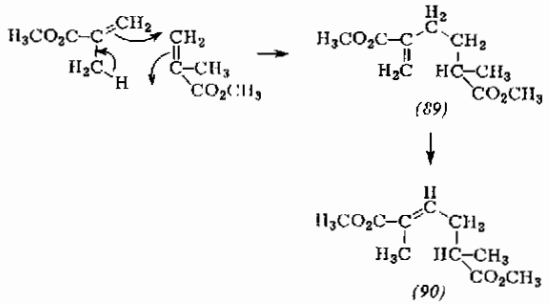
R = Na, CH_3

It is also possible that interactions between the d-orbitals of the sulfur and the π-electrons of the double bond are involved in compounds such as *(83)*. Any such interaction would not be very pronounced since the electron-attracting properties of one ester or carboxyl group attached to the C=C double bond are smaller than those of two nitrile groups.

In the infrared spectrum, the C=C double-bond band of α,β-bis(alkylthio)acrylic acids occurs at 1517–1530 cm^{-1} [57,97]; this indicates the strong displacement to longer wavelengths which is generally observed in vinyl thioethers [103–105]. The C=C double-bond band in β,β-bis(methylthio)acrylic acid lies at 1514 cm^{-1}, and that of β,β-bis(benzylthio)acrylic acid acid at 1500 cm^{-1} [57].

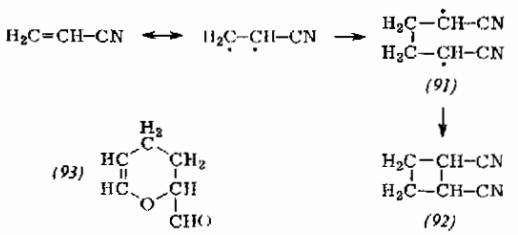
2. The Mechanism of the Dimerization of Acrylic Acid Derivatives

The "head-to-head" dimerizations described in Section B,1.a also occur to some extent with the corresponding unsubstituted acrylic acid derivatives, although by no means as readily. Thus, acrylonitrile gives a small yield of cyclobutane-1,2-dicarbonitrile *(92)* only at 200 °C [106]. No head-to-head dimerization of unsubstituted acrylic esters has yet been discovered. Methacrylic ester dimerizes to α-methyl-α'-methyleneadipic ester *(89)*, which is partially converted by an allylic rearrangement into α,α'-dimethyl-α,β-dihydromuconic ester *(90)* [107].

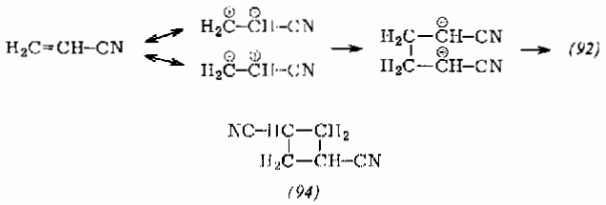


Since alkylthioacrylic esters contain no allylic groupings, they cannot undergo an "ene" synthesis of this type. This is also true for the reaction of methacrylic ester with maleic anhydride [86,87,108].

Coyner and *Hillman* [106] postulated that the cyclodimerization of acrylonitrile proceeds via the 1,4-diradical *(91)*, by analogy to the dimerization of acrolein to *(93)*. The latter may be regarded as a diene synthesis [88].



In their discussion of the mechanism of thermal cyclodimerizations, *Roberts* and *Sharts* [109] note that an explanation of the head-to-head dimerization of acrylonitrile via such a 1,4-diradical mechanism is preferable to a polar mechanism, because the latter requires that a fraction of the acrylonitrile molecules taking part in the cyclodimerization to *(92)* is in a polarized state opposite to that normally assumed, otherwise head-to-tail dimerization to *(94)* would occur.



[101] *G. Bähr* and *G. Schleitzer*, Chem. Ber. *90*, 438 (1957).

[102] *H. E. Simmons, D. C. Blomstrom*, and *R. D. Vest*, J. Amer. chem. Soc. *84*, 4756 (1962).

[103] *H. J. Boonstra* and *L. C. Rinzema*, Recucil Trav. chim. Pays-Bas *79*, 962 (1960).

[104] *P. P. Shorygin, M. F. Shostakovsky, E. N. Prileshayeva, T. N. Shkurina, L. G. Stolyarova*, and *A. P. Genitsch*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1961*, 1571.

[105] *H. J. Schneider, J. J. Bagnell*, and *G. C. Murdoch*, J. org. Chemistry *26*, 1987 (1961).

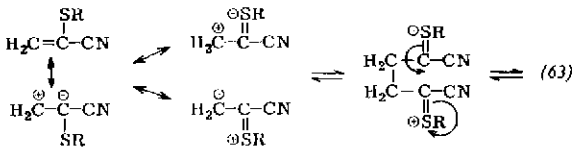
[106] *E. C. Coyner* and *W. S. Hillman*, J. Amer. chem. Soc. *71*, 324 (1949).

[107] *C. J. Albisetti, D. C. England, M. J. Hogsed*, and *R. M. Joyce*, J. Amer. chem. Soc. *78*, 472 (1956).

[108] *K. Alder, F. Pascher*, and *A. Schmitz*, Ber. dtsch. chem. Ges. *76*, 27 (1943).

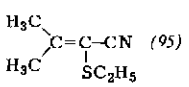
[109] *J. D. Roberts* and *C. M. Sharts* in: Organic Reactions. Wiley, New York 1962, Vol. XII, p. 1.

On the other hand, because of their ability to act both as electron donors and as acceptors, thioether groups should greatly facilitate a polar mechanism, and thus the dimerization as well.

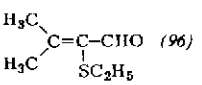


(63)

Thus, the positive character of the β-carbon atom, which is imparted by the nitrile group and which is already present in unsubstituted acrylonitrile itself can be reinforced by a thioether group. This effect is in fact significant as may be seen from the fact that α-methylthiocrotononitrile and α-methylthiocinnamonitrile, in which hyperconjugative or mesomeric charge compensation is possible, do not cyclodimerize [78,80]. The nitrile *(95)*, which is prepared from the very stable aldehyde *(96)* [110], apparently behaves in the same manner.



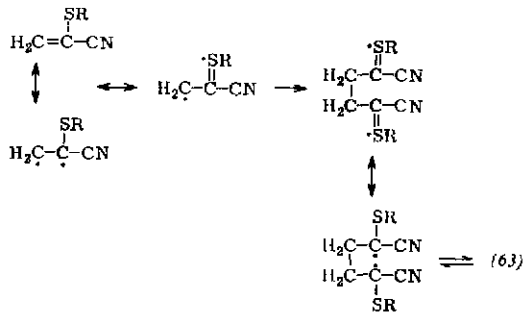
(95)



(96)

However, the thioether groups facilitate not only a polar mechanism but also a 1,4-diradical mechanism, because the presence of thioether groups allows delocalization of the free electron from the α-carbon atom to the sulfur atom [111]. β-Alkyl or aryl groups would then also have a deactivating effect as in the polar mechanism.

The same applies for head-to-head dimerization of the α-alkylthioacrylic esters and the α-alkylthioacroleins. However, here the 1,4-zwitterions or 1,4-diradicals formed as intermediates would become stabilized as other end products, namely dihydromuconic esters *(67)* and dihydropyrans *(76)*, respectively [82,83,106].



(63)

No dimerizations have been reported so far for α-alkoxy- [112–114] and α-dialkylaminoacrylic acid derivatives [115,116]. Indeed, even the usual addition reactions onto C=C double bonds, such as those of amines [114], either fail to occur here or proceed different [112,114,117] from those of the α-alkylthioacrylic acid derivatives. This also supports the conclusion that the special reactivity of the α-alkylthioacrylic acid derivatives is caused by the ability of the thioether group to act both as electron donor and electron acceptor.

Received, April 3rd, 1963 [A 312/117 IE]
German version: Angew. Chem. 75 (1963), to appear in December.

[110] *J. H. Sperna-Weiland* and *J. F. Arens*, Recueil Trav. chim. Pays-Bas *75*, 1358 (1956).

[111] *C. E. Scott* and *C. C. Price*, J. Amer. chem. Soc. *81*, 2670 (1959).

[112] *T. Cuvigny*, Bull. Soc. chim. France *1957*, 655.

[113] *J. Monnin*, Chimia *11*, 337 (1957).

[114] *J. Monnin*, Helv. chim. Acta *40*, 1983 (1957).

[115] *H. Glaser* in *Houben-Weyl*: Methoden der organischen Chemie. Thieme, Stuttgart 1957, Vol. XI/1, p. 184. German Pat. 700861 (1938), I.G. Farbenindustrie, inventors: *H. Lange*, *H. Kranz*, and *O. Nicodemus*.

[116] *S. C. Temin*, J. org. Chemistry *22*, 1714 (1957).

[117] *K.-D. Gundermann* and *R. Huchting*, unpublished data.

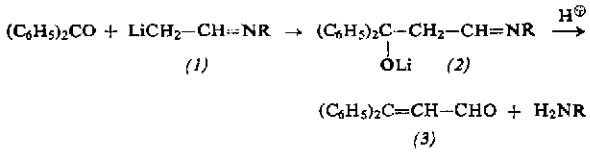
COMMUNICATIONS

Directed Aldol Condensations

By Prof. Dr. G. Wittig, cand. chem. H. D. Frommeld, and cand. chem. P. Suchanek

Institut für Organische Chemie der Universität Heidelberg (Germany)

Previously, it was not possible to direct the aldol condensation of an aldehyde with a ketone under the usual conditions in such a way as to effect specific combination of the CH_2-group of the aldehyde with the ketonic carbonyl group in order that subsequent dehydration of the resulting aldol to the α,β-unsaturated aldehyde might be achieved [1]. It was appreciated in quite a different connection [2] that this is actually possible. If, instead of the aldehyde, the corresponding Schiff's base is used as starting material and is metallated with lithium diethylamide in ether, self-condensation of the aldehyde is circumvented under mild conditions; the resultant organometallic compound *(1)* adds on smoothly to benzophenone to give *(2)*, which on acidic hydrolysis affords the unsaturated aldehyde *(3)* in good yield.



(1) *(2)* *(3)*

The following method proved to be convenient and generally applicable: cyclohexylamine was used to prepare the Schiff's base of acetaldehyde, and lithium diisopropylamide was used as metallating agent. The crystalline adduct *(2)* (m.p. 127 to 128 °C) was formed in 92 % yield and was converted in 81 % yield (based on the benzophenone) into α-phenylcinnamaldehyde *(3)*, m.p. 45–46 °C, by treatment with dilute sulfuric acid. As the aldol adducts are usually crystalline, the acidic hydrolysis to the unsaturated carbonyl compound can be carried out under controlled conditions. Table 1 gives details of the yields of other directed aldol condensations (molar ratio of reactants 1:1).

Table 4.

Reactants	(2) Yield [%]	(2) M.p. [°C]	(3)
$(C_6H_5)_2CO$ + C_2H_5–CH=NR	91	82–83	
$(C_6H_5)_2CO$ + CH_3–CH–CH–CH=NR	22	156–157	
C_6H_5–CO–CH_3 + CH_3–CH=NR	80	60–61	65 % β-Phenylcrotonaldehyde (b.p. 125–130 °C/13 mm) + 22 % methyl styrene
β-Ionone + CH_3–CH–NR	80	46–47	42 % β-Ionylideneacetaldehyde (b.p. 115–120 °C/ 10^{-3} mm)
C_6H_5–CHO + CH_3–CH–NR	94	79–80	77 % Cinnamaldehyde (b.p. 117–120 °C/12 mm)
Cyclohexanone + CH_3–CH=NR	92	62–62.5	58 % Cyclohexylideneacetaldehyde (semicarbazone, m.p. 208–209 °C)

The reaction of *(1)* with halides (in a molar ratio of 1 : 1) gives extended Schiff's bases (see Table 2).

Table 2.

Halide	Schiff's base	B.p. [°C/12 mm]	Yield [%]
CH_3I	CH_3–CH_2–CH=NR	62–63	51
$C_2H_5C_2H_5I$	C_2H_5–CH_2–CH–NR	80–82	69
H_2C–CH–CH_2Br	H_2C–CH–CH_2–CH_2–CH=NR	98–100	60
C_6H_5–CH_2Cl	C_6H_5–CH_2–CH_2–CH=NR [*]		

[*] Gives dihydrocinnamaldehyde (b.p. 102–104 °C/13 mm) in 51 % yield on treatment with dilute HCl.

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Publication delayed until now at the request of the authors.
German version: Angew. Chem. *75*, 978 (1963)

[1] Cf. *O. Bayer* in *Houben-Weyl*: Methoden der organischen Chemie. Thieme, Stuttgart 1954, Vol. VII, part 1, p. 76 et seq.

[2] *G. Wittig, H.-J. Schmidt*, and *H. Renner*, Chem. Ber. *95*, 2377 (1962).

A New Type of Automatic Redox Titrator

By Dr. P. Boldt and Dr. H. Lackner [1]

Organisch-Chemisches Institut der Universität Göttingen (Germany)

Dedicated to Prof. Dr. Hans Brockmann on the occasion of his 60th birthday

Redox potentials of organic compounds are usually established only very slowly. They cannot be determined accurately with conventional automatic titrators, since these usually add the titrating solution relatively fast or in increments at preselected time intervals, which are frequently insufficient for the establishment of equilibrium. Our automatic redox titrator adds fresh titrating solution only after equilibrium has been established. This is achieved by storing the measured potential (after amplification) in a condenser located in the control mechanism. The potential is again measured after an adjustable, preselected time interval (checking time) and stored in a second condenser. The stored potentials are then compared in the monitor. If their values are different, equilibrium has not yet been attained and no further addition of titrating solution takes place. If equilibrium has been reached, the potentials in the two condensers will be equal. The monitor then records a point on the titration curve and energizes a dosage pump to add a measured quantity of titrating solution.

This control sequence is periodically repeated until the entire titration is recorded. The equilibration times for the individual equilibrium potentials can be quite different throughout the process. Since the sensitivity of the monitor can also be altered, it is also possible to determine automatically the normal potentials of compounds with equilibrium potentials which are established only very slowly. In this way we have, for instance, found the normal redox potential of 7-hydroxyactinomycin C_1 [2], which is of interest in connection with the bonding of actinomycins onto DNA [3], to be +204 mV.

A number of redox potential determinations were replicated in order to determine the reprodicibility of the results (cf. Table 1).

Table 1. Redox potentials of some compounds.

Compound	E_H found [a] [+ mV]		E_0 literature value [+ mV]	
2,5-Dihydroxybenzoquinone	437	438	433	435 [b]
2-Hydroxynaphthoquinone	359	360	356	357 [b]
5-Hydroxynaphthoquinone	450	451	452	452 [b]
lin-Naphthindazole-4,9-quinone	154	155 [c]	154.1	154.8 [d]

[a] In 0.5 N HCl (50 % ethanol), relative to 1,4-naphthoquinone (E_0 = +483.5 mV).

[b] *J. B. Conant* and *L. F. Fieser*, J. Amer. Chem. Soc. *46*, 1858 (1924), found deviations of a few mV between their measurements and the calculated values.

[c] Measured by Dr. *T. Reschke*.

[d] *L. F. Fieser* and *M. A. Peters*, J. Amer. chem. Soc. *53*, 4080 (1931), measured in 70 % ethanol + 0.5 N HCl + 0.2 N LiCl.

The deviation from the mean of single measurements was within ± 2 mV (evaluated from 10 titrations); the time for one titration was between 6 and 8 hours.

Received, June 18th, 1963 [Z 572/402 IE]
German version: Angew. Chem. *75*, 978 (1963)

[1] Detailed description: Chemie-Ing.-Techn. *35*, 707 (1963).

[2] *H. Brockmann* and *H. Peterssen-Borstel*, unpublished work; *H. Peterssen-Borstel*, Diploma Thesis, Universität Göttingen 1961; the authors wish to thank Dr. *Werner Müller* for supplying the material.

[3] *W. Müller*, Naturwissenschaften *49*, 159 (1962).

Dimethyl Sulfate Complexes of N-Monoalkylformamides

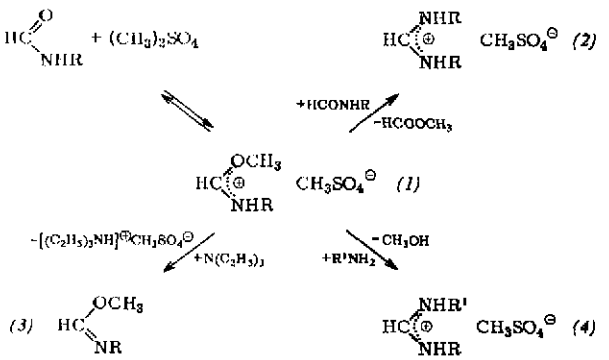
By Prof. Dr. H. Bredereck, Dr. F. Effenberger, and Dipl.-Chem. Erika Henseleit

Institut für Organische Chemie und Organisch-chemische Technologie der Technischen Hochschule Stuttgart (Germany)

On treatment of *N*-alkylformamides with an excess of dimethyl sulfate (ca. 2 moles) [1], we obtained very good yields of methyl *N*-alkylformiminate/methyl sulfate complexes [*(1)*, R = CH_3: n_D^{20} = 1.4513, 95 % yield; R = C_2H_5: n_D^{20} = 1.4525, 80 %]. An excess of amide gave *N,N'*-dialkylformamidinium methyl sulfates *(2)* by way of *(1)*. Examples: *(2)*, R = CH_3: n_D^{20} = 1.4665, 95 %; m.p. of picrate 169 °C [2]; R = C_2H_5: n_D^{20} = 1.4583, 96 %, m.p. of picrate 123.5–124.5 °C [3].

Acyl chloride complexes of *N*-alkylformamides yield isonitriles with bases and thus do not react with nucleophilic partners [4]. In contrast, no isonitrile is formed with the

O-alkyl methyl sulfate salts *(1)* which, therefore, can react with nucleophilic partners.



On reaction of *(1)* with triethylamine we obtained methyl *N*-alkylformiminates [*(3)*, R = CH_3: n_D^{20} = 1.3875, m.p. 47–49 °C; R = C_2H_5: n_D^{20} = 1.3881, m.p. 61–63 °C] for the first time. Care is needed in dealing with these new substances. Compound *(1)* and primary amines interact to give the (also previously unknown) unsymmetrical *N,N'*-dialkylformamidinium methyl sulfates [*(4)*, R' = C_2H_5, R = CH_3: n_D^{20} = 1,4556; m.p. of picrate 111–112 °C; R' = n–C_4H_9, R = CH_3: n_D^{20} = 1.4554; R' = C_6H_{11}, R = C_2H_5: n_D^{20} = 1.4813]. The free amidines are obtained from these under mild conditions but rearrange at higher temperatures to the symmetrical amidines.

Received, July 5th, 1963 [Z 540/361 IE]
German version: Angew. Chem. *75*, 790 (1963)

[1] For reactions of formamide and *N,N*-disubstituted formamides with dialkyl sulfates, see *H. Bredereck* et al., Chem. Ber. *92*, 329 (1959); *96*, 1351 (1963).

[2] *G. Simchen*, Ph.D. Thesis, Technische Hochschule Stuttgart, 1962; *E. C. Taylor* and *W. A. Ehrhardt*, J. org. Chemistry *28*, 1108 (1963).

[3] *J. W. Cornforth:* The Chemistry of Penicillin. Princeton University Press, 1949, p. 851.

[4] *J. Ugi* and *R. Meyr*, Chem. Ber. *93*, 239 (1960); *J. Hagedorn* and *H. Tönjes*, Pharmazie *12*, 570 (1957).

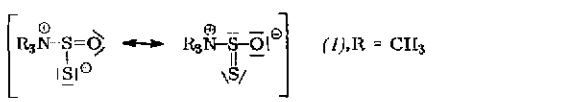
Adducts of Disulfur Monoxide

By Prof. Dr. P. W. Schenk and cand. chem. R. Steudel

Anorganisch-Chemisches Institut der Technischen Universität Berlin and Institut für Anorganische Chemie der Freien Universität Berlin (Germany)

Disulfur monoxide is strongly unsaturated owing to its S=S double bond [1] and polymerizes readily to polysulfur oxides with partial decomposition to SO_2 [2]. Stabilization of monomeric S_2O can be achieved by nucleophilic addition of amines with sharing of the 3d-orbitals of the sulfur. Trimethylamine reacts with S_2O to yield intense lemon-yellow, crystalline $S_2O{\cdot}N(CH_3)_3$ *(1)*, which separates out at −30 °C/2 mm total pressure. At +20 °C, *(1)* decomposes slowly into trimethylamine, SO_2, and sulfur.

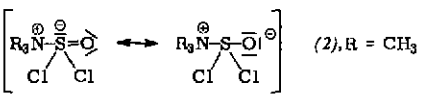
The yellow color of *(1)* indicates its partial double bond character.



Compound *(1)* sublimes *in vacuo* above −10 °C. Free S_2O can be detected in the vapor by means of its ultraviolet spectrum. In this way, reversible vaporization of condensed S_2O has been attained for the first time.

$N(C_2H_5)_3$ and NH_3 form similar yellow adducts with S_2O; these then react further to yield red secondary products.

$SOCl_2{\cdot}N(CH_3)_3$ *(2)* was obtained analogously from its components by fractional condensation at −30 °C. Compound *(2)* forms colorless crystals, sublimes *in vacuo* above −20 °C, and hydrolyses quantitatively to HCl, SO_2, and trimethylamine



S_2O forms very unstable adducts by electrophilic addition of BF_3. Condensation of the components at −160 °C yielded bordeaux-red $S_2O{\cdot}nBF_3$ (n = 2 or 3), which could be freed from excess BF_3 only by thermal decomposition *in vacuo* at −140 °C. $SO_2{\cdot}BF_3$ [3], on the other hand, was stable under these conditions at −150 °C.

Received, July 8th, 1963 [Z 545/374 IE]
German version: Angew. Chem. *75*, 793 (1963)

[1] *P. A. Giguere*, J. physic. Chem. *64*, 190 (1960).

[2] *P. W. Schenk*, Z. anorg. allg. Chem. *233*, 385 (1937).

[3] *H. S. Booth* and *D. R. Martin*, J. Amer. chem. Soc. *64*, 2198 (1942).

Amides and Imides of Tetravalent Titanium and Zirconium

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The amides of trivalent titanium, chromium, and cobalt were previously obtained as amorphous precipitates from solutions of $K_3[Ti(SCN)_6]$ [1], $[Cr(NH_3)_6](NO_3)_3$, and $[Co(NH_3)_6](NO_3)_3$[2] in liquid amonia by precipitation with the equivalent quantity of KNH_2. Analogous preparations of the amides of tetravalent titanium and zirconium were attempted.

$Ti(NO_3)_4$ *(1)*, obtained according to *Schmeisser* [3] by treating $TiCl_4$ with N_2O_5, dissolves in liquid ammonia with partial ammonolysis to give a yellow solution. Small ammounts of orange-yellow material $Ti(NH_2)_{2.83}(NH)_x(NO_3)_{1.17}$ (x = 1.08–1.15) precipitate. The reaction of *(1)* with KNH_2 (1:4) leads to a brown product corresponding almost exactly to the formula $Ti(NH_2)_4$. On passing nitrogen even at −78 °C over this compound, the color deepens and NH_3 is split off leading to the formation of the imide, which could not be analyzed owing to its explosive nature.

Crystalline $Zr(NO_3)_4{\cdot}2HNO_3$, which still contains HNO_3 and which is prepared from zirconium hydroxide and nitric acid, is not suitable for the preparation of $Zr(NH_2)_4$ since in liquid NH_3 it forms a heterogeneous precipitate containing Zr, N, and O. By treating $ZrCl_4$ with KSCN in acetonitrile, $K_2[Zr(SCN)_6]{\cdot}CH_3CN$ *(2)* was obtained; this loses all of its CH_3CN on heating to 90 °C *in vacuo*. The acteonitrile-free complex salt dissolves in liquid NH_3 to give a pale yellow solution; on evaporating the NH_3, $K_2[Zr(SCN)_6]{\cdot}4\ NH_3$ is left as residue.

On addition of KNH_2 to a solution of acetonitrile-free *(2)* (4:1), a pale yellow precipitate results, which, after standing in a current of nitrogen at 22 °C has the composition $Zr(NH)_2$. This imido is amorphous and, in contrast to the titanium compound, is not explosive.

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German version: Angew. Chem. *75*, 792 (1963)

[1] *O. Schmitz-DuMont* and *G. Broja*, Z. anorg. allg. Chem. *258*, 307 (1949).

[2] *O. Schmitz-DuMont*, *J. Pilzecker*, and *H. F. Piepenbrink*, Z. anorg. allg. Chem. *248*, 175 (1941).

[3] *M. Schmeisser*, Angew. Chem. *67*, 493 (1955).

Alkynyl Derivatives of Aluminum

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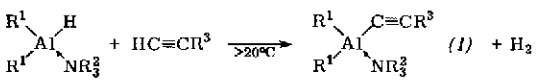
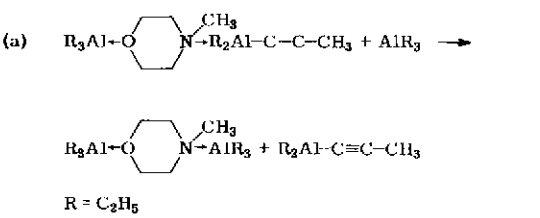
Mülheim-Ruhr (Germany)

Trialkylaminates of dialkylaluminum hydride react smoothly with 1-alkynes at 20–40 °C in excess trialkylamine to give the aminates of dialkylalkynylaluminum *(1)*.



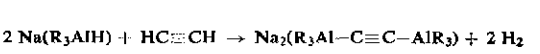
Similarly, both hydrogen atoms of acetylene can be smoothly the R_2Al-group, a stable monoaminate with double molecular weight being formed. At 100–120 °C, trialkylaluminum trialkylaminates also give *(1)*, R^1H being eliminated. The known addition of Al–H- and Al–C-bonds onto triple bonds [1] does not occur in the presence of amines. In contrast, etherates of dialkylaluminum hydride react with 1-alkynes only above 100 °C, but then addition of the alkynes onto the triple bond occurs predominantly as a result of dissociation of $R_2AlH{\cdot}OR_2$. Etherates of trialkylaluminum do not react under these conditions.

The free dialkylalkynylaluminum compounds can be obtained from the aminates by exchange with trialkylaluminum as shown in (a) for the propynyl derivative.



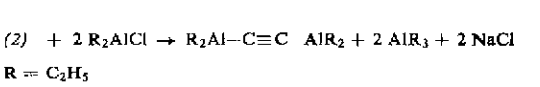
$R = C_2H_5$

Diethylpropynylaluminum (b.p. 50 °C/0.001 mm) and bis-(triethylaluminum)-*N*-methylmorpholine (b.p. 90 °C/0.001 mm) can be readily separated by distillation. Alkali trialkylalanates [$M(R_3AlH)$] react smoothly with 1-alkynes at 50–60 °C without any catalyst (diethylamine [2], lithium hydride [3]) to give $M(R_3AlC{\equiv}CR)$. Both hydrogen atoms of acetylene react and it is not possible to stop the reaction at the stage of monosubstitution [$M(R_3AlC{\equiv}CH)$].



(2)

The reaction of sodium bis(triethylaluminum)acetylene *(2)* with diethylaluminum chloride gives 1,2-bis(diethylaluminum)acetylene, a white powder which is insoluble in hydrocarbons.



This compound, which is probably polymeric as a result of association via Al–C_2–Al-bridges, forms a monoetherate of double molecular weight.

Received, August 2nd, 1963 [Z 559/401 IE]
German version: Angew. Chem. 75, 918 (1963)

[1] *G. Wilke* and *H. Müller* Liebigs Ann. Chem. *629*, 222 (1960).

[2] *G. B. Smith, D. H. McDaniel, E. Biehl*, and *C. A. Hollingsworth*, J. Amer. chem. Soc. *82*, 3560 (1960).

[3] *P. Chini, A. Baradel, E. Pauluzzi*, and *M. De Malde*, Chim. e Ind. *44*, 1220 (1962); Chem. Abstr. *58*, 13973h (1963).

Preparation of Germyl-lithium Diammoniate and Potassium Dihydrogen Antimonide

By Priv.-Doz. Dr. E. Amberger and Dr. H. Boeters

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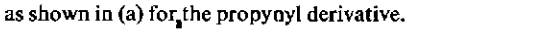
der Universität München (Germany)

Germane reacts quantitatively with lithium in liquid NH_3 to yield germyl-lithium diammoniate *(1)*.

Gaseous germane is passed into a solution of lithium in NH_3 just above the melting point of the mixture (−77.7 °C) until decolorization occurs (after about 45 min for 0.005 g-atom of Li). The vapor pressure of GeH_4 at −77 °C (1350 mm of Hg) is greater than that of NH_3 (48 mm). The NH_3 is then sublimed off at −78.2 °C to leave *(1)* as a pale grey, stable solid. On warming *(1)* to room temperature, ammonia (2 moles) is evolved and a melt is formed above a solid phase. On standing for some time at 20 °C, or more quickly by heating at 250 °C, the solid phase decomposes with evolution of hydrogen and change of color from yellow, through brown, to red. Germane is not liberated.

Stibine reacts quantitatively with potassium in liquid NH_3 to form potassium dihydrogen antimonide *(2)*.



However, it is not possible to introduce gaseous stibine into the metal solution at −77 °C, since it has a lower vapor pressure at −77 °C (34 mm) than NH_3 has. If excess stibine is condensed over the frozen solution of the metal, antimony separates out. These inconveniences can be avoided if the stibine is passed into the metal solution at −77 °C at a partial pressure of about 10 mm together with propane until decolorization occurs (50 min for 0.01 g-atom of K). The hydrogen released into the gaseous mixture can de determined readily by freezing out the C_3H_8 and NH_3. The NH_3 is then sublimed off at −78.2 °C. A residue of *(2)* remains as a stable, red-brown solid. On warming to room temperature, its color changes to black, with evolution of hydrogen.

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German version: Angew. Chem. 75, 860 (1963)

Heterocyclics from Ethoxymethylenecyanamide and Ethoxymethyleneurethane

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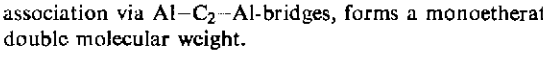
Ethoxymethylenecyanamide *(1)* and ethoxymethyleneurethane *(2)* are obtained in 85 and 90 % yield respectively by heating cyanamide or urethane with orthoformic ester [in the presence of a little BF_3 for *(2)*]

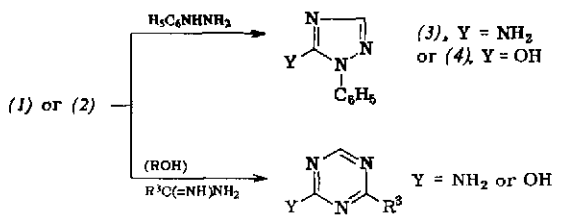


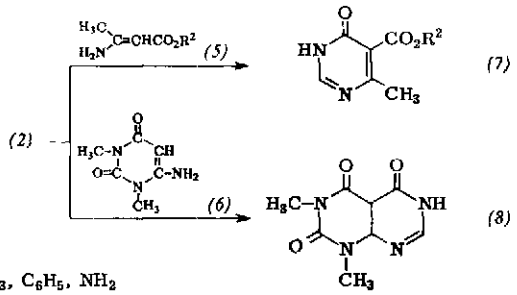
(1): $R^1 = CN$; $R^2 = C_2H_5$
(2): $R^1 = CO_2R^2$; $R^2 = C_2H_5$

and are suitable starting materials for simple syntheses of 1,2,4-triazoles, *s*-triazines, and pyrimidines.

5-Amino-1-phenyl-1,2,4-triazole *(3)* is obtained in 60 % yield from *(1)* and phenylhydrazine in boiling benzene. In the analogous reaction with *(2)*, phenylhydrazinomethyleneurethane is initially formed (71 %) and on heating in diphenyl

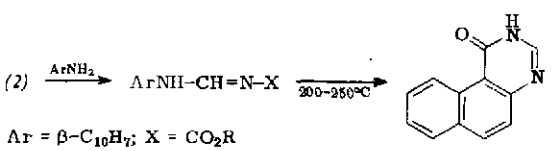
ether is cyclized to 1-phenyl-1,2,4-triazol-5-one *(4)* (yield: 81 %). 1,2,4-Triazol-5-one results directly from *(2)* and hydrazine in 60 % yield.





s-Triazines are not only obtained from open-chain amidines; *N*-α-pyridyl-*N'*-ethoxycarbonylformamidine, which is prepared almost quantitatively by heating α-aminopyridine with *(2)* to approx. 100 °C, is converted on addition to boiling diphenyl ether into pyrido[1,2-*a*]-*s*-triazin-4-one in 41 % yield.

In contrast to tautomerizable enamines, such as β-aminocrotonic ester *(5)* or 1,3-dimethyl-4-aminouracil *(6)*, which react directly with *(2)* at 100–120 °C to yield pyrimid-4-ones [*(7)* in 40 % yield, *(8)* in 86 % yield], aromatic primary amines react with *(2)* to yield formamidines; their cyclization to quinazol-4-ones requires heating in diphenyl ether.



The yields are sometimes satisfactory (Ar = α-naphthyl, 51 %; β-naphthyl, 89 %; 2-anthryl, 94 %), but occasionally poor (Ar = C_6H_5, 10 %); now and then merely decomposition of the formamidine is observed.

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German version: Angew. Chem. *75*, 918 (1963)

Syntheses with Tris(alkylarylthio)carbenium Salts

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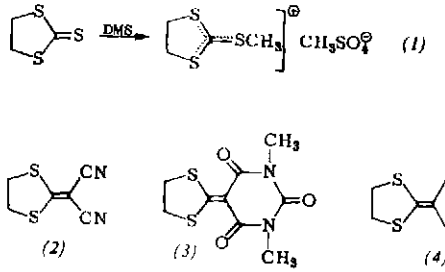
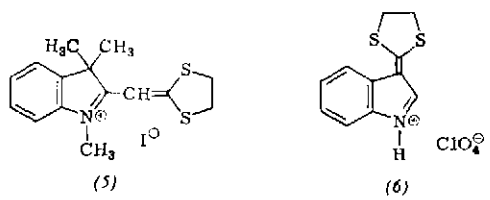
A new route to ketene mercaptals [1, 2] uses tris(alkylarylthio)carbenium salts as intermediates. The latter are readily obtained by heating trithiocarbonic acid esters with alkylating agents (dimethyl sulfate, ethyl tosylate *etc.*). The carbenium salts react readily, on heating in pyridine/triethylamine or glacial acetic acid/pyridine, with compounds possessing sufficiently acidic methylene groups or with phenols. Thus *(1)* reacts with malononitrile to give *(2)* (90 % yield), with 1,3-dimethylbarbituric acid to give *(3)* (84 % yield), and with 2,6-di-t-butylphenol to give *(4)* (47 % yield). Similarly *(1)* reacts with dimedone, 2-hydroxy-1,4-naphthoquinone, anthrone and β-naphthol.



Compound *(1)* is very reactive. This is shown by the fact that polyhydric phenols (contrary to the reaction of their alkali salts with carbon disulfide [2]) react according to the number of hydroxyl groups. Thus 3 moles of *(1)* react with phloroglucinol in 83 % yield. Under the same conditions, *(1)* reacts with enamines, *e.g.* with 1,3,3-trimethyl-2-methylene-indoline to give *(5)* in 30 % yield, with indole to give *(6)* in 41 % yield, and with tertiary aromatic amines, such as *N*,*N*-dimethylaniline [3].



2-Methylthio-1,3-benzdithiolium methyl sulfate *(7)* reacts with phenols even more readily than *(1)*. By reaction of *(7)* with phenol, *S*,*S'*-phenylene-ω,ω-dimercapto-*p*-benzoquinone methide [4] is formed in 75 % yield. The condensation of trithionium salts with dimethylaniline could not be applied to phenols [5].

Tris(methylthio)- and methylthiobis(phenylthio)carbenium methyl sulfate (from dimethyl or diphenyl trithiocarbonate, respectively, and dimethyl sulfate) form crystal violet with dimethylaniline. They react, although more slowly than *(7)* and *(1)*, with compounds possessing active methylene groups and with phenols.

Received, August 15th, 1963 [Z 567/391 IE]
German version Angew. Chem. *75*, 919 (1963)

[1] *R. Gompper* and *W. Töpfl*, Chem. Ber. *95*, 2861 (1962).

[2] *R. Gompper* and *R. Schmidt*, Angew. Chem. *74*, 780 (1962); Angew. Chem. internat. Edit. *1*, 596 (1962).

[3] Reaction of 2-methylthio-5-methyl-1,3-benzdithiolium perchlorate with dimethylaniline: see *L. Soder* and *R. Wizinger*, Helv. chim. Acta *42*, 1733, 1779 (1959).

[4] Preparation see *W. R. Hurtley* and *S. Smiles*, J. chem. Soc. (London) *1926*, 1821; *1927*, 534.

[5] *U. Schmidt*, *R. Scheuring*, and *A. Lüttringhaus*, Liebigs Ann. Chem. *630*, 116 (1960).

A Macrocyclic Azo Dye

By Dipl.-Ing. J. Jarkovský and Dr. Z. J. Allan

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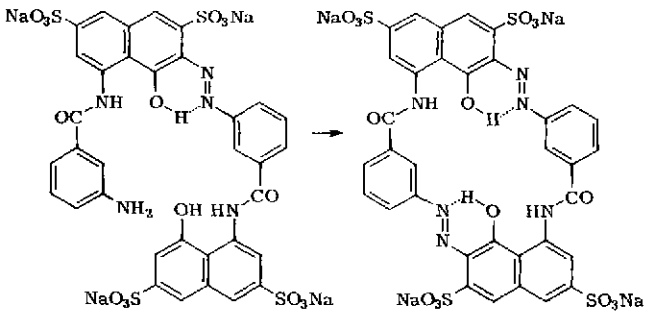
We have found that a cyclic azo dyestuff is formed in quantitative yield when compounds with suitably spaced groups and suitable bond angles are reacted according to the Ruggli-Ziegler dilution principle. 1-(*m*-Aminobenzoylamino)-8-hydroxynaphthalene-3,6-disulfonic acid [1] was coupled with its diazonium derivative in aqueous $NaHCO_3$. The azo compound *(1)* was precipitated with NaCl and purified by crystallization (from acetone/water 1:9). One millimole of *(1)* was di-

azotized and added dropwise over 1 hour at 10 °C to a solution of 1.06 g of Na_2CO_3 in 500 ml of water. Judging from paper chromatograms (isoamyl alcohol/pyridine/5 % ammonia 1:1:1), the cyclic disazo compound *(2)* is obtained almost exclusively (R_F = 0.07; R_F for *(1)* is similar) with only traces of polymeric dyes ($R_F \approx 0$). After evaporating the solution to one-tenth of the original volume, the product was precipitated with NaCl and recrystallized from water. When the second coupling is carried out in a 50 times more concentrated solution, the yield falls to about 50 %. The remainder consists of polymer.



(1) *(2)*

Dyestuff *(2)* forms red-brown needles (tetrahydrate after drying at 130 °C), dissolves in water to give a red solution (maxima at 333 and 490 mμ). Upon hydrolysis of *(2)* with 10 % hydrochloric acid, one or both amide bonds are split to give free carboxylic acids *(3)* or *(4)*. Reductive cleavage with sodium dithionate yields only one product, *viz.* 1-(*m*-Aminobenzoylamino)-7-amino-8-naphthol-3,6-disulfonic acid. In contrast to *(1)*, *(2)* does not react with naphthalenediazonium-4-sulfonic acid. Compounds *(1)*, *(3)*, and *(4)* and the polymeric dyestuffs dissolve in water to give bordeaux-red solutions.

Received, August 19th, 1963 [Z 575/400 IE]
German version: Angew. Chem. 75, 979 (1963)

[1] *I. E. Balaban* and *H. King*, J. chem. Soc. (London) *1927*, 3068.

Cyclododecanone Oxime and Cyclo-octanone Oxime from Cyclododecatriene and Cyclo-octadiene

By Dr. H. Metzger

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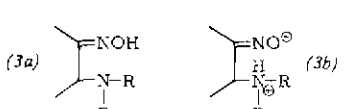
The addition of nitrosyl chloride onto cyclododecatriene normally yields a mixture of positional isomers of bis(chloronitrosocyclododecadiene) with the nitroso group and chlorine atom on adjacent positions [1]. In the presence of hydrogen chloride, however, nitrosyl chloride reacts with cyclododecatriene to give structural isomers of chlorohydroximinocyclododecadiene *(1)*, likewise with adjacent substituents.

In the case of the *trans,trans,cis*-compound, a *trans*-bond is preferentially attacked. Cyclo-octa-1,5-diene behaves in exactly the same way; only one mole of nitrosyl chloride is added and 1-chloro-2-hydroximinocyclo-octene *(2)* is formed. Both α-chloro-oximes can be converted into the hydroximinoamines *(3a)* or *(3b)* by treatment with secondary amines.



(3a) *(3b)*

Hydrogenation of *(1)* in the presence of noble-metal catalysts at 40–50 °C and atmospheric pressure in methanol, for example, proceeds smoothly to give cyclododecanone oxime as major product. Palladium is especially suitable as catalyst; if platinum is used, cyclododecylamine may be the major product.

In contrast, hydrogenation of *(2)* or of α-chlorocyclo-octanone oxime with palladium or platinum affords a mixture of cyclo-octanone oxime and cyclo-octanone together with cyclo-octylamine, the Schiff's base from cyclo-octylamine and cyclo-octanone, and traces of α-aminoethylcyclohexane.

Received, August 23rd, 1963 [Z 577/408 IE]
German version: Angew. Chem. 75, 980 (1963)

[1] German Published Patent Application 1094741 (1959) Studiengesellschaft Kohle, inventors: *E. Wilke*, *E. W. Müller*, and *J. Stedefeder*. Our results indicate that the NOCl adducts described by *L. I. Zakharkin*, U.S.S.R. Pat. 139317 (1960), are dimeric nitroso compounds.

A Photochemical 1,2-Hydrogen Shift in the Cyclohepta-1,3,5-triene Molecule

By Dr. R. Roth

Institut für Organische Chemie der Universität Köln (Germany)

Although thermal excitation of cyclohepta-1,3,5-triene gives primarily a 1,5-hydrogen shift [1], bicyclo[3,2,0]hepta-2,6-diene [2] and toluene [3] have been described as the products of photochemical excitation. By irradiating 7-deuterocyclohepta-1,3,5-triene (95 % C_7H_7D) in methanol with a high-pressure mercury lamp in a Pyrex apparatus, we were able to show that the valence isomerization is preceded by a 1,2-hydrogen shift.

The first change in the NMR spectrum of the 7-deuterocyclohepta-1,3,5-triene was observed after an irradiation time of 30 min and is the superposition of a doublet, the lines of which have a fine structure, on the 1:2:1-triplet of the aliphatic hydrogen atoms (split at this stage into a 1:1:1-triplet by D(7)-H(7)-coupling). The intensity of this new signal reaches a maximum after ca. 4 hours; it then falls off to a constant value corresponding to statistical distribution of the deuterium. The primary occurrence of a doublet is characteristic for a methylene group which possesses only one α-hydrogen atom and indicates a 1,2-hydrogen shift, the intramolecular character of which was demonstrated by mass-spectroscopic analysis of the photolysis products.

Similarly, photolysis of 7-methyl- and 7-ethylcyclohepta-1,3,5-triene (1 % in methanol, Pyrex apparatus, high-pressure Hg lamp) gives primarily 1-methyl- and 1-ethylcyclohepta-1,3,5-triene; the structures of these compounds were proved by hydrogenation to methyl- and ethylcycloheptane respectively, and by their NMR spectra which contained a doublet at 7.65 and 7.75 τ due to the two H(7)-hydrogen atoms. Irradiation of 7-vinylcyclohepta-1,3,5-triene even for a short time gives only traces of 1-vinylcycloheptatriene, as this is very rapidly converted by a 1,2-hydrogen shift into the 2- and 7-vinyl isomers as a result of its ultraviolet absorption at longer wavelength (λ_{max} = 298 mμ; ε = 7000).

Hydrogen migration during the gas-phase photolysis of 7-methoxycyclohepta-1,3,5-triene was also recently observed [4].

Received, August 28th, 1963 [Z 578/407 IE]
German version: Angew. Chem. 75, 921 (1963)

[1] *C. Grundmann* and *G. Ottmann*, Liebigs Ann. Chem. *582*, 163 (1953); *G. Büchi* and *E. M. Burges*, J. Amer. chem. Soc. *84*, 3104 (1962); *A. P. Ter Borg*, *H. Kloosterziel*, and *N. Van Meurs*, Proc. chem. Soc. (London) *1962*, 359.

[2] *W. G. Dauben* and *R. L. Cargill*, Tetrahedron *12*, 186 (1961).

[3] *R. Srinivasan*, J. Amer. chem. Soc. *84*, 3432 (1962).

[4] *O. L. Chapman* and *G. W. Borden*, Proc. chem. Soc. (London) *1963*, 221.

Rearrangement of N-Methyl-1,2-dihydropapaverine with Dilute Acids

By Priv.-Doz. Dr. J. Knabe, Dr. J. Kubitz, and N. Ruppenthal

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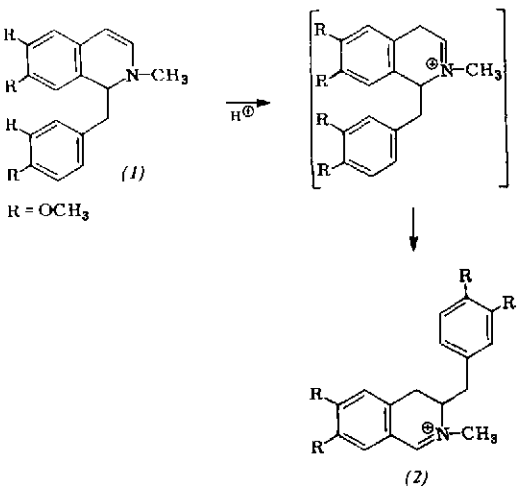
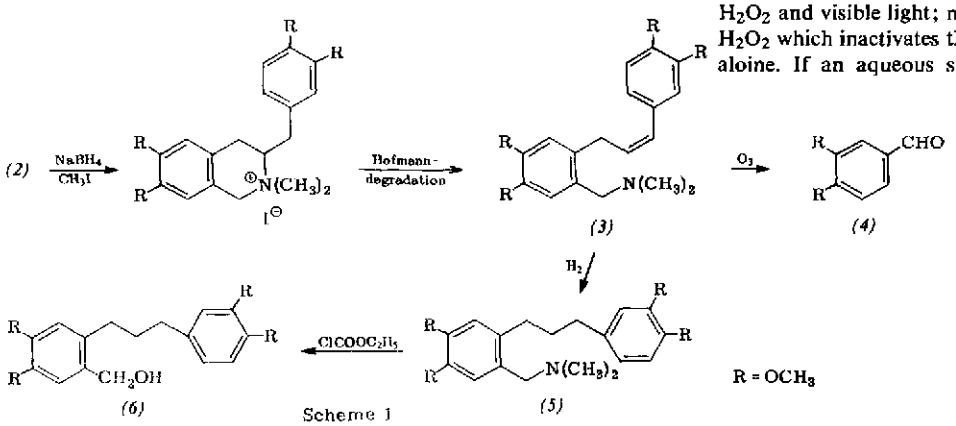
N-Methyl-1,2-dihydropapaverine *(1)* is irreversibly altered by acids [1]. *Battersby* and *Binks* [2] obtained *N*-methylpavine by heating *(1)* for 25 hours in a mixture of phosphoric and formic acids. We have found that when *(1)* is heated with dilute acids on the water-bath, it rearranges to *(2)*, with a shift of the isolated C=N double bond to become conjugated with the aromatic system and with migration of the substituent on C-1.



Compound *(2)* reacts with KCN to give a "pseudocyanide", m.p. 115–117 °C. The constitution was elucidated by degradation according to Scheme 1.



Scheme 1

On ozonisation, the methine base *(3)* yields veratraldehyde *(4)* as a neutral fission product. Being a phenylogous *O,N*-acetal, the hydrogenated methine base *(5)* may be split with ethyl chloroformate [3], forming the alcohol *(6)*, which was characterized as the phenylurethane (m.p. 115–116 °C). The phenylurethane of the alcohol *(6)* made in another way and that of the degradation product agreed in m.p., mixed m.p., and infrared spectrum.

Received, Sept. 3rd, 1963 [Z 576/403 IE]
German version: Angew. Chem. *75*, 981 (1963)

[1] *H. Schmid* and *P. Karrer*, Helv. chim. Acta *32*, 960 (1949).

[2] *A. R. Battersby* and *R. Binks*, J. chem. Soc. (London) *1955*, 2888.

[3] Cf. *J. Knabe* and *U. R. Shukla*, Arch. Pharmaz. *295*, 690 (1962).

Photoreactivation in the Presence of Hydrogen Peroxide

By Prof. Dr. A. Wacker and Andrea Gerstenberger

Institut für Therapeutische Biochemie der Universität Frankfurt a. M. (Germany)

Respectfully dedicated to Professor Otto Warburg on the occasion of his 80th birthday

Most biological radiation damage caused by ultraviolet light can be reversed by irradiation with visible light (photoreactivation). For this purpose, an enzyme (enzyme complex?) is necessary [1]. We were able to show that the lethal effect of ultraviolet light on the cell is due predominately, if not exclusively, to radiochemical dimerization of the thymine in DNA [2]. On photoreactivation, the thymine-dimer in the DNA is split again into monomeric thymine [2].

Table 1. % Survivors of *E. coli* B after treatment with various agents [a].

Bacteria treated with:						
Ultraviolet light	Energy [erg/mm²]	H_2O_2	Amount [µg/ml]	Visible light [b]	Energy [erg/mm²]	Survivors [%]
–	–	–	–	[c]		100
+	10	–	–	–	–	59
–	–	+	3	[c]		66
+	10	+	3	–	–	80
+	10	–	–	+	5×10^5	80
+	10	+	3	+	5×10^4	87
+	10	+	3	+	5×10^5	99

[a] The bacteria were exposed to the agents at the end of logarithmic growth in the nutrient medium [*A. Wacker, M. Ebert,* and *H. Kolm*, Z. Naturforsch. *13b*, 141 (1958)] after dilution 1:1000000. Composition of agar: Difco tryptone 1 %, Difco yeast extract 0.1 %, NaCl 0.25 %, $CaCl_2$ 0.02 %, Difco agar 1.5 %.

[b] Daylight lamp HPR 125 W.

[c] Dayligth.

As is shown in Table 1, bacteria inactivated by ultraviolet light can be almost completely reactivated by treatment with H_2O_2 and visible light; moreover, this occurs with a dose of H_2O_2 which inactivates the bacterial cells when administered aloine. If an aqueous solution of the thymine-dimer is irradiated with visible light in the presence of 3 % hydrogen peroxide, a decomposition of the thymine-dimer is observed.

From these and other findings (no radiochemical transformation of the thymine-dimer with H_2O_2 in ice, no photoreactivation in the frozen state, decomposition of the thymine-dimer in the presence of H_2O_2 by heat, and thermal reactivation of UV-inactivated bacterial cells), we conclude that the photoreactivation is possibly connected with the formation of H_2O_2 and oxygenous radicals, which are formed by biological oxidizing enzymes on irradiation with visible light.

Received, September 13th, 1963 [Z 579/404 IE]
German version: Angew. Chem. *75*, 916 (1963)

[1] *J. Jagger* in: Radiation Protection and Recovery. Pergamon Press, London 1960, p. 352 et seq.

[2] *A. Wacker* in: Progress in Nucleic Acid Research. Academic Press, New York, London 1963, Vol. 1, p. 369 et seq.

Uridine-(5′→3′)-uridine-5′-pyrophosphate as Substrate for Polynucleotide Phosphorylase

By Prof. Dr. F. Cramer, Dipl.-Ing. H. Küntzel, and Dipl.-Ing. S. Rittner

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An enzyme which is probably identical with nucleoside monophosphate kinase [1] is ipresent in a crude extract from *Azotobacter vinelandii*. It catalyses the following reaction [2]:

ATP + pUpU ⇌ ADP + ppUpU
(1) *(2)*

In the presence of urea, the two pyrophosphates arising as intermediates, *viz.* ADP and *(2)*, [*(2)*: $R_F = 0.42$ in isopropanol/ammonium sulfate 2:1, ascending; $R_F = 0.16$ on a polymine thin-layer [3] with 0.5 M NaCl] are polymerized to polyadenylic-uridylic acid by the polynucleotide phosphorylase which is also found in the bacterial extract. In the presence of 1 M urea, phosphorolytic cleavage of the dinucleotide by polynucleotide phosphorylase and thus the subsequent incorporation of uridylic acid via UDP as intermediate are prevented. Similarly, urea inhibits the phosphorolysis of polyadenylic-uridylic acid [4].

The structure of the synthetically prepared [5] dinucleotide *(1)* (R_F = 0.045 in isopropanol/conc. ammonia/water 7:1:2) was proved by cleavage with ribonuclease; the sole products are uridine-3′,5-diphosphate *(3)* and uridine.

pUpU → pUp + Uridine
(1) *(3)*

Incubation medium: 3 μM of *(1)*, 3 μM of ATP, 60 μM of tris buffer at pH 8,1. 6 μM of $MgCl_2$, 300 μM of urea, 0.01 ml of crude enzyme extract (29 mg of protein per ml); final volume: 0.3 ml; temperature: 30 °C. After an incubation time of 24 hr, the polymer was isolated and subjected to alkaline hydrolysis with 0.3 M KOH at 37 °C for 20 hr; the hydrolysate was neutralised with $HClO_4$ and was separated by paper chromatography into 3′(2′)-AMP and 3′(2′)-UMP; 0.4 μM of ADP and 0.22 μM of *(2)* had been incorporated.

In a control experiment (same medium, but without ATP), no cleavage products of *(1)* could be detected after 24 hr.

The polynucleotide must consequently have a structure such as the following:

...pUpUpA(pA)pUpUpA(pA)pUpU...

Further experiments with purified enzymes and with mixed oligonucleotides are in progress.

Received, September 13th, 1963 [Z 580/405 IE]
German version: Angew. Chem. 75, 981 (1963)

[1] *I. Lieberman, A. Kornberg,* and *E. S. Simms,* J. biol. Chemistry *215*, 429 (1955).

[2] pUpU *(1)* = uridine-(5′→3′)-uridine-5′-phophate, *(2)* = uridine-(5′→3′)-uridine-5′-pyrophosphate.

[3] *K. Randerath:* Thin-Layer Chromatography. Verlag Chemie, Weinheim, and Academic Press, New York 1963, p. 195.

[4] *F. Cramer* and *H. Küntzel,* Biochim. biophysica Acta, in the press.

[5] *S. Rittner,* unpublished work.

On the Composition of the Tungsten Compounds Formed by Reaction of Tungsten Bromide with Phenyl-lithium

By Prof. Dr. B. Sarry and Dipl.-Ing. M. Dettke

Anorganisch-Chemisches Institut der Technischen Universität Berlin (Germany)

Tungsten pentabromide reacts with an etheral solution of phenyl-lithium to give an organometallic compound which was prepared by *Hanke* and given the formula $W(C_6H_5)_3 \cdot 3LiC_6H_5 \cdot 3(C_2H_5)_2O$ [1]. *Hanke* [2] determined the Li content by solvolysis of the compound, addition of excess acid, and back titration of the H^+-ions.

By direct acidimetric titration of the alkaline solution obtained on solvolysis we now found two pH steps, the first of which occurred after two equivalents and the second after a third equivalent of acid had been added. In addition, we determined the lithium in the titrated solution by flame photometry and found an atomic ratio of Li:W = 2:1. Neutralization of the LiOH produced by hydrolysis gives rise to the first pH step. By back titration, the sum of all the H^+-ions used up is obtained. The compound prepared by *Hanke*'s method has two phenyl-lithium groups per tungsten atom. Since it dissolves without dissociation, as shown by molecular weight determinations, it is best represented as $W(C_6H_5)_4 \cdot (LiC_6H_5)_2 \cdot 3(C_2H_5)_2O$. This formula is in accordance with the measured diamagnetism of the compound.

Received, September 16th, 1963 [Z 581/410 IE]
German version: Angew. Chem. 75, 1022 (1963)

[1] *H. Funk* and *W. Hanke,* Angew. Chem. *71*, 408 (1959).
[2] *W. Hanke,* Ph. D. Thesis, Universität Halle 1959; *B. Sarry,* Angew. Chem. *71*, 776 (1959).

Perchlorocyclobutenone — a New Synthesis of Four-Membered Rings

By Dr. G. Maaß

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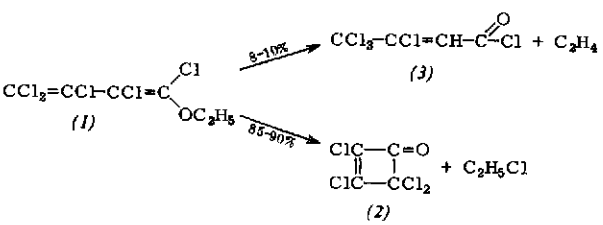
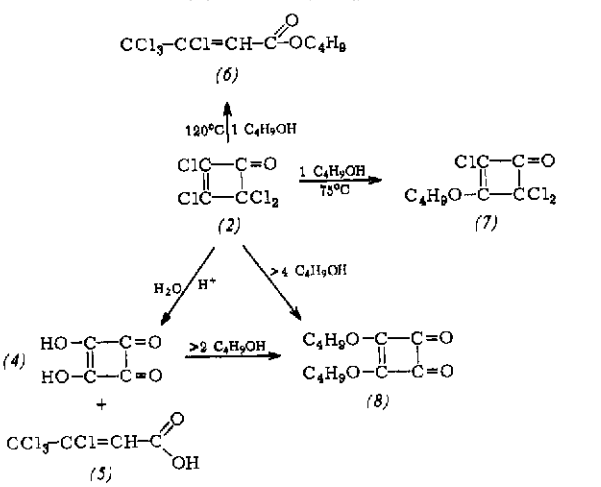
Marl, Kreis Recklinghausen (Germany)

1-Ethoxypentachloro-1,3-butadiene *(1)* [1] is converted into the previously unknown compound perchlorocyclobutenone *(2)* by heating to ca. 200 °C (85–90 % conversion; 85–90 % yield; b.p. 58 °C/10 mm, 174–176 °C/760 mm; $n_D^{20} = 1.5303$). Elimination of ethylene in a side-reaction gives α*H*-tetrachlorocrotonyl chloride *(3)* (8–10 % yield; b.p. 55 °C/4 mm; $n_D^{20} = 1,5298$).



Hydrolysis of *(2)* with sulfuric acid affords 3,4-dioxocyclobutene-1,2-diol *(4)* ("squaric acid") [2] and α*H*-tetrachlorocrotonic acid *(5)* [with 20 % H_2SO_4 at 100 °C without



Scheme 1. Protolytic reactions of perchlorocyclobutenone.
(6) = butyl α*H*-tetrachlorocrotonate: b.p. 116 °C/3 mm; $n_D^{20} = 1.4952$;
(7) = 1-butoxy-2,4,4-trichlorocyclobuten-3-one: b.p. 110 °C/2.5 mm; $n_D^{20} = 1.5101$;
(8) = dibutyl ester of "squaric acid" (1,2-dibutoxy-3,4-dioxocyclobutene): b.p. 139 °C/0.5 mm; $n_D^{20} = 1.4932$.

stirring: 57 mole-% of *(4)* plus 42 mole-% of *(5)*; with 98 % H_2SO_4 and dropwise addition of the theoretical amount of H_2O with stirring at 110 °C: 90 mole-% of *(4)*, 3 mole-% of *(5)*]. Compound *(4)*, m.p. 292 °C (decomp.), is a strong acid in aqueous solution and gives sparingly soluble salts with numerous heavy metals. Further reactions of *(2)* are shown in Scheme 1.

Received, September 24th, 1963 [Z 584/412 IE]
German version: Angew. Chem. 75, 982 (1963)

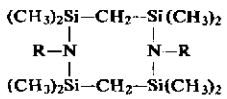
[1] *A. Roedig* and *P. Bernemann*, Liebigs Ann. Chem. *600*, 1 (1956).
[2] *J. D. Park, S. Cohen*, and *J. R. Lacher*, J. Amer. chem. Soc. *84*, 2919 (1962).

Aminosilanes and Silazanes with Si—CH_2—Si Groups

By Dr. K. Lienhard and Prof. Dr. E. G. Rochow

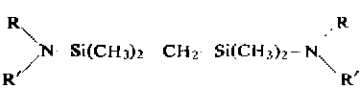
Department of Chemistry, Harvard University, Cambridge, Massachusetts (U.S.A.)

$Br-Si(CH_3)_2-CH_2-Si(CH_3)_2-Br$ *(1)* [1] reacts with NH_2R (R = H or CH_3) to form derivatives of 1,3,5,7-tetrasila-2,6-diazacyclo-octane, a new heterocyclic ring system.



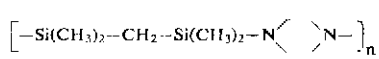
(2) R = H: B.p. 82—84 °C/3.5 mm; m.p. 35 °C
(3) R = CH_3: B.p. 97 °C/3 mm; m.p. 44—45 °C

The compounds were purified by vacuum sublimation. They are rapidly solvolysed by water and alcohols. On heating *(2)* in the presence of NH_4Br, 0.66 mole of NH_3 is split off. Compound *(1)* reacts with methylamine at −50 °C firstly to form *(4)*, which loses CH_3NH_2 on heating under reflux for several hours, some of it condensing to give *(3)*.



(4) R = H, R' = CH_3: B.p. 50.0 50.5 °C/6 mm; $n_D^{30} = 1.4404$
(5) R = R' = C_2H_5: B.p. 76–77 °C/3 mm; $n_D^{23} = 1.4535$

Compound *(5)* is prepared from *(1)* and diethylamine and can undergo transamination with piperazine, whereby elimination of diethylamine occurs and the polymer



is formed ($n \approx 14$).

Infrared and NMR spectra of the compounds were recorded.

Received, September 17th, 1963 [Z 582/411 IE]
German version: Angew. Chem. 75, 980 (1963)

[1] *K. Lienhard* and *E. G. Rochow*, Angew. Chem. 75, 638 (1963); Angew. Chem. internat. Edit. 2, 325 (1963).

The Toxicity of Metal Carbonyl Derivatives

By Prof. Dr. W. Strohmeier

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Our laboratory is concerned mainly with the photochemical preparation of metal carbonyl derivatives [1]. We were, therefore, interested in the toxicity of this type of compound. We prepared a number of compounds and had them tested on mice (Table 1). We intend to continue these toxicity tests on further compounds.

The substances were administered by intravenous injection in polyethylene glycol 200, and the results were evaluated by known statistical methods [2].

Table 1. Toxicities of metal carbonyl derivatives in the mouse test.

	Substance	DL_{50} [mg/kg]	"Confidence limits" [mg/kg]
(1)	Cycloheptatriene-$Cr(CO)_3$	0.708	0.501—1.00
(2)	Cycloheptatriene-$Mo(CO)_3$	>20.0	
(3)	Toluene-$W(CO)_3$	>20.0	
(4)	Toluene-$Cr(CO)_3$	5.62	1.78—17.8
(5)	Toluene-$Mo(CO)_3$	>20.0	
(6)	Chlorobenzene-$Cr(CO)_3$	1.78	0.562—5.62
(7)	*p*-Dichlorobenzene-$Cr(CO)_3$	5.62	1.78—17.8
(8)	*p*-Dimethoxybenzene-$Cr(CO)_3$	>20.0	
(9)	*p*-Xylene-$Mo(CO)_3$	>20.0	
(10)	1,3,5-Trimethylbenzene-$Cr(CO)_3$	>20.0	
(11)	Piperidine-$Cr(CO)_5$	0.708	0.562—0.891
(12)	Piperidine-$W(CO)_5$	0.631	0.501—0.796

The substances *(1)*, *(4)*, *(6)*, *(11)*, and *(12)* caused death of the animals within 0.5-3 minutes. The large difference between the toxicities of *(1)* and *(2)* is of interest, because these two compounds show hardly any difference in their chemical and physico-chemical properties, and the ligands are linked in the same way.

These preliminary experiments do not yet allow any connection to be recognized between the ligand and the toxicity of the metal carbonyl derivatives. Caution is therefore advisable, also when working with analogous compounds. The question of the toxicity on inhalation as vapor or dust has not yet been examined. Molybdenum hexacarbonyl is known to be only weakly toxic *per os*, whereas a dust concentration of only 0.7 mg/l is lethal to rabbits within 10 to 30 minutes.

Received, September 25th, 1963 [Z 590/421 IE]
German version: Angew. Chem. 75, 1024 (1963)

[1] *W. Strohmeier* and *J. F. Guttenberger*, Chem. Ber. *96*, 2112 (1963), where further references are given.
[2] *J. T. Sitchfield* and *F. Wilcoxen*, J. Pharm. exp. Therapeut. *96*, 99 (1949).

The Chemistry of Selenium Trioxide

By Prof. Dr. Max Schmidt, Dr. P. Bornmann, and Dr. Irmgard Wilhelm

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der Universität Marburg/Lahn (Germany)

Because of the extreme reactivity of selenium trioxide and the explosive nature of its reaction with oxidizable substances, no solvent for it was so far [1] known. We managed to dissolve preparative quantities of SeO_3 unchanged in acetic anhydride, diethyl ether, dioxan, or liquid sulfur dioxide by first purifying it by sublimation *in vacuo* at ca. 120 °C. SeO_3 can be recovered unaltered from SO_2, whereas evaporation *in vacuo* of its saturated solution in ethers (33 mg/ml and 88 mg/ml, respectively) leaves the monoetherates $SeO_3 \cdot (C_2H_5)_2O$ (decomp. 59 °C) and $SeO_3 \cdot C_4H_8O_2$ (decomp. ca. 65 °C). SeO_3 can be transferred smoothly from the etherates over to stronger bases such as pyridine to give $SeO_3 \cdot C_5H_5N$ (m.p. 148 °C). Solutions of SeO_3 in SO_2 are particularly suitable for the selenation of hydrocarbons, *e.g.* benzeneselenonic acid is formed smoothly in 80 % yield. In ether, SeO_3 decomposes on treatment with H_2S at low temperatures, but thiols and thiophenols form derivatives of the new compound thioselenic acid, which can be isolated as mono etherates or

$$SeO_3 + RSH \rightarrow RS-SeO_3H \quad (R = C_4H_9-, C_7H_9-, C_6H_5-) \qquad (1)$$

sodium salts (from NaOR). $(C_2H_5)_2S$ leads to the formation of $(C_2H_5)_2S \cdot SeO_3$.

Chloroselenic acid *(1)*, the existence of which was not considered possible, is formed in SO_2.

$$SeO_3 + HCl \rightarrow \underset{(1)}{ClSeO_3H} \qquad (2)$$

It can also be obtained directly, although not as easily, without a solvent (white crystals decomposing above −10 °C). Its silyl esters are more stable and can be obtained in ether from R_3SiCl and SeO_3 by analogy to Equation (2), or from *(1)* and R_3SiCl with elimination of HCl. Compound *(1)* and absolute H_2O_2 give HCl and a quantitative yield of the previously unknown peroxomonoselenic acid, H_2SeO_5, a white solid that is stable up to 0 °C.

$$(1) + H_2S \rightarrow HCl + HSSeO_3H \qquad (3)$$

In ether, *(1)* and H_2S react to give free thioselenic acid which is considerably less stable even than free thiosulfuric acid. Its *S*-mono-esters can be obtained not only according to Equation (1), but also from *(1)* and thiols by elimination of HCl. The *O*-mono esters are produced by thiolysis of the silyl esters of *(1)* mentioned above.

$$(CH_3)_3SiOSeO_2Cl + H_2S \rightarrow (CH_3)_3SiOSeO_2SH + HCl \qquad (4)$$

When working with SeO_3 and its derivatives, greatest precautions must be taken to exclude moisture, and only mildest conditions may be employed; strictest safety measures must also be used because of the danger of explosions on mixing SeO_3 with organic substances!

Received, October 2nd, 1963 [Z 588/416 IE]
German version: Angew. Chem. 75, 1024 (1963)

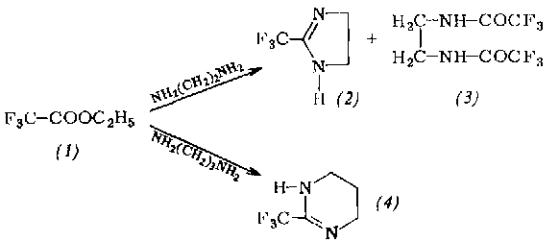
[1] *F. Toul* and *K. Dostál*, Collect. czechoslov. chem. Commun. *16*, 571 (1951); *H. A. Lehmann* and *G. Krüger*, Z. anorg. allg. Chem. *267*, 324 (1952); *K. Dostál* and *I. Krejči*, ibid. *296*, 29 (1958).

2-Trifluoromethyl-Δ^2-imidazoline and 2-Trifluoromethyl-Δ^2-tetrahydropyrimidine

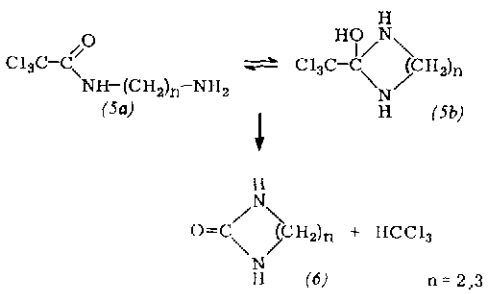
By Priv.-Doz. Dr. H. Baganz and Dr. L. Domaschke

Organisch-Chemisches Institut
der Technischen Universität Berlin (Germany)

In comparison with a previous publication [1], the reactions of ethyl trifluoroacetate and ethyl trichloroacetate with aliphatic diamines [2] such as ethylene diamine and trimethylene diamine which we carried out gave different results. The reaction of ethyl trifluoroacetate *(1)* with ethylene diamine without solvent [1] gave solely the diacyl compound *(3)*; in alcoholic solution, however, a second product, *viz.* 2-trifluoromethyl-Δ^2-imidazoline *(2)*, m.p. 110–112 °C (subl.), was now obtained in 15 % yield in addition to *(3)*. The reaction of *(1)* with trimethylene diamine in alcoholic solution gives 2-trifluoromethyl-Δ^2-tetrahydropyrimidine *(4)*, m.p. 108–110 °C (subl.), in 56 % yield.



Ethyl trichloroacetate reacts with ethylene diamine in the molar ratio 2:1 to give 1-trichloroacetyl-2-trichloromethyl-Δ^2-imidazoline [1]. If the reaction is carried out in alcoholic solution with excess diamine, chloroform and the cyclic urea derivative *(6)* are formed. As a result of the ring-chain tautomerism observed with trichloroacetyl derivatives of bifunctional compounds [3], the haloform may be eliminated from either the open-chain form *(5a)* or the cyclic form *(5b)*.



The haloform elimination thus competes with the known cyclization reaction with elimination of water to give cyclic amides.

Received, October 2nd, 1963 [Z 589/417 IE]
German version: Angew. Chem. 75, 1025 (1963)

[1] *M. M. Jouillie* and *A. R. Day*, J. Amer. chem. Soc. *76*, 2990 (1954).

[2] Aliphatic diamines with trifluoroacetonitrile: see *R. N. Johnson* and *H. M. Woodburn*, J. org. Chemistry *27*, 3958 (1962).

[3] *H. Meerwein* and *H. Sönke*, Ber. dtsch. chem. Ges. *64*, 2375 (1931); *H. Hibbert* and *M. Greig*, Canad. J. Chem. *1931*, 254; see also Chem. Zbl. *1931*, I, 3666 and Ber. dtsch. chem. Ges. *65*, 199 (1932).

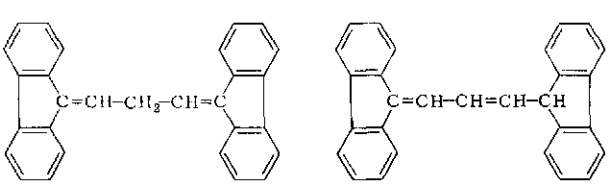
CONFERENCE REPORTS

The Pentatetraene Problem

By *Richard Kuhn* and *Herbert Fischer*, Heidelberg (Germany)

1. Synthetic Experiments (reported by *R. Kuhn*).

All the pentatetraenes described so far in the literature apparently do not possess this kind of structure. This was proved for example for the so-called 1,5-di-t-butyl-1,5-diphenylpentatetraene [1] and for the so-called tetraphenylpentatetraene [2]. The evasion reactions (addition of two hydrogen atoms; ring-closure to form indene derivatives; dimerization; dimerization with addition of four hydrogen atoms) lead mostly to compounds which display non-aromatic vinyl protons in the nuclear magnetic resonance spectrum, in disagreement with the cumulene structure. Pentadienes were prepared as intermediates for the synthesis of pentatetraenes. In proton-activating solvents such as dimethylformamide and dimethyl



1,4-diene, m.p. 199–200 °C
λ_{max} = 317 mμ; *ca.* 17 %

1,3-diene, m.p. 179–180 °C
λ_{max} = 350 mμ; *ca.* 83 %

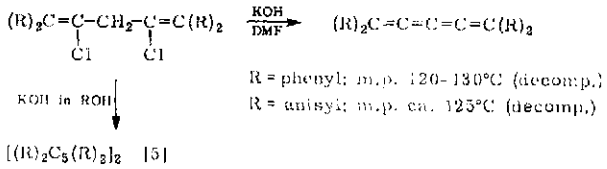
[1] *R. Kuhn* and *B. Schulz*, Angew. Chem. *74*, 292 (1962); Angew. Chem. internat. Edit. *1*, 211 (1962).

[2] *R. Kuhn* and *B. Schulz*, Angew. Chem. *75*, 452 (1963); Angew. Chem. internat. Edit. *2*, 395 (1963).

sulfoxide, pentadienes were shown [3] to establish an equilibrium via migration of the double bonds, *e.g.*

The energy of activation found was 15 kcal/mole.

In the solvents mentioned, alkali hydroxides remove two moles of hydrogen halide from 2,4-dihalogenopentadienes within a few minutes even at room temperature forming genuine monomolecular pentatetraenes [4]. In methanol or ethanol it is necessary to boil for half an hour and only a dimeric product is obtained, *e.g.*



Tetraanisyl- and tetraphenylpentatetraene (which crystallize in needles) show no non-aromatic vinyl protons in the nuclear magnetic resonance spectrum and take up 4.0 moles of hydrogen on hydrogenation over Raney-nickel. In accordance with *H. Fischer*'s predictions from quantum theory [6], their color is lighter than that of the corresponding trienes.

Unlike the corresponding butatriene and hexapentaene, tetraanisylpentatetraene is readily protonated to give a violet cation, *e.g.* even on dissolution in acetic acid. With iodine it yields a dark-violet crystalline periodide $C_{33}H_{28}IO_4^{\oplus}I_3^{\ominus}$; the infrared spectrum of the latter contains a strikingly strong peak at 4.85 μ (*W. Otting*).

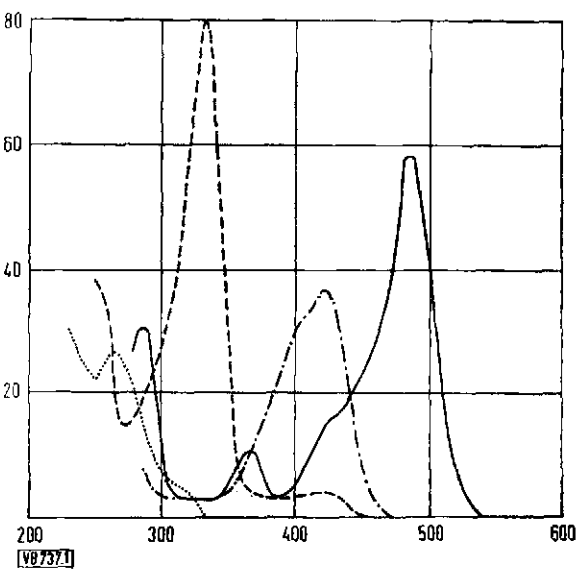


Fig. 1. Absorption spectra of some cumulenes.
.... Tetraphenylallene
---- Tetraphenylbutatriene
---- Tetraphenylpentatetraene
Tetraphenylhexapentaene
Ordinate: Extinction coefficient × 10^{-3}
Abscissa: Wavelength [mμ].

2. Quantum-mechanical Calculations (reported by *H. Fischer*):

If the excitation energies for tetraphenylcumulenes are calculated according to *Hückel*'s theory and compared with the principal long-wave bands measured (Fig. 1), than the good agreement apparent from the correlation diagram (Fig. 2) is obtained between theory and experiment. The weak foreband

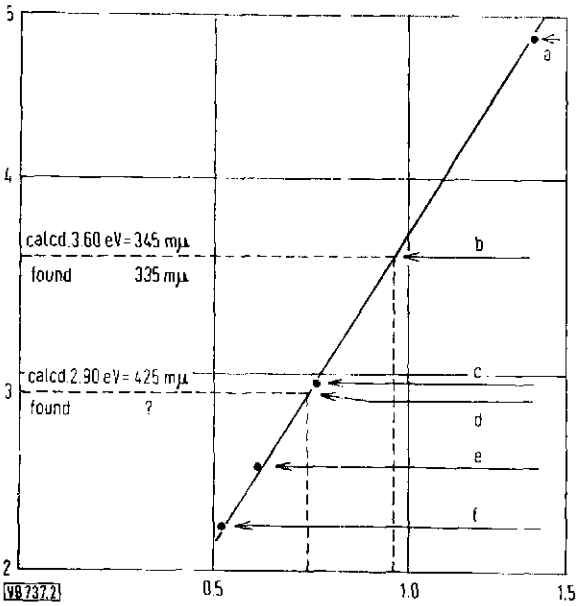


Fig. 2. Correlation diagram for tetraphenylcumulenes.
a = allene, b = pentatetraene, c = butatriene, d = heptahexaene, e = hexapentaene, f = octaheptaene.
Ordinate: Energy of the measured absorption bands [eV].
Abscissa: Calculated excitation energy in β.

in tetraphenylpentatetraene at 420 mμ (Fig. 1; for tetraanisylpentatetraene it lies at 434 mμ) can be explained by slight interaction between the two normally independent π-systems, whose nodal planes are perpendicular to one another in tetraphenylpentatetraene (two 1,1-diphenylbutadiene π-systems). The degeneracy in the energy levels is removed by such interaction, and besides the absorption bands calculated according to the elementary *Hückel* theory, a long-wave and a short-wave band are always obtained as well. However both should have much smaller intensities than the main band. The energy levels of butatriene and hexapentaene are not degenerate. Slight interaction between the two independent π-systems will therefore have scarcely any effect in these systems. Tetraanisylallene and tetraanisylpentatetraene are far more readily protonated than the corresponding butatriene and hexapentaene (formation of deeply-colored cations, *e.g.* by addition of a little perchloric acid to their solution in acetone). This is explained by the fact that the difference in π-electron energy between the cumulene and the protonated cumulene is considerably larger for butatrienes and hexapentaenes than for allenes and pentatetraenes.

[Colloquium held in the Max-Planck-Institut für Medizinische Forschung, Heidelberg (Germany), July 22nd, 1963] [VB 737/103 IE]

German version: Angew. Chem. 75, 870 (1963)

Synthesis of Heterocyclics from Isothiocyanates

J. Goerdeler, Bonn (Germany)

Alkyl, aryl, and acyl isothiocyanates add onto primary and secondary enamines of the type of α-aminocrotonic ester *(1)* and β,β-diaminoacrylic ester *(2)*. On oxidation, these adducts yield 5-aminoisothiazoles *(3)* or 5-iminoisothiazolines *(4)*.

The following deviations from the normal course of reaction were observed: 1) addition of the isothiocyanate onto the amino group; 2) abnormal course of the cyclo-dehydrogenation of certain addition compounds of aryl isothiocyanates and dimedone-imine, resulting in benzthiazole derivatives; 3) compounds from enamines and acyl isothiocyanates may be converted by spontaneous or base-catalysed dehydration into

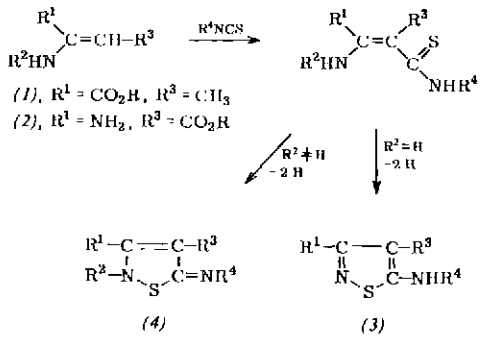
[3] Experiments by *D. Rewicki*.

[4] Experiments by *Herbert Fischer* and *Hans Fischer*.

[5] Structure still unknown; cf. *R. Kuhn, H. Fischer, F. A. Neugebauer*, and *H. Fischer*, Liebigs Ann. Chem. *654*, 64 (1962).

[6] In *S. Patai*: The Chemistry of the Alkenes. In the press; manuscript submitted on March 1st, 1963.

thiopyrimidones. The corresponding derivatives of phenoxycarbonyl isothiocyanate decompose with loss of phenol and yield thiouracil derivatives. This new pyrimidine synthesis has so far proceeded smoothly in all cases.

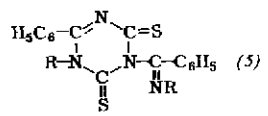


(1), $R^1 = CO_2R$, $R^3 = CH_3$
(2), $R^1 = NH_2$, $R^3 = CO_2R$

(4) *(3)*

The von Pechmann synthesis of substituted 5-amino-1,2,3-thiadiazoles may be extended to diazoacetic ester, diazoacetamide, and diazoketones, when acyl isothiocyanates are employed. In the simplified procedure, the appropriate acid chloride is added dropwise to a solution of the diazoacetic ester and sodium thiocyanate. The use of phenoxycarbonyl isothiocyanate with subsequent mild alkaline hydrolysis affords primary 5-amino-1,2,3-thiadiazoles, which may be acylated, sulfonated, and diazotized.

Imidoyl isothiocyanates (prepared from imidoyl chloride and alkali thiocyanate) dimerize spontaneously to red high-melting compounds, for which structure *(5)* is assumed. This is another case of 1,4-addition of an X–C–N=C–Y system.



(5)

[GDCh-Ortsverband Nordwürttemberg, Stuttgart (Germany), June 27th, 1963] [VB 732/100 IE]

German version: Angew. Chem. *75*, 941 (1963)

Fulminate Complexes

W. Beck, München (Germany)

All the fulminato-complexes of transition metals known [1] have the same type of structure as the homologous cyano-compounds. Recent examples include $[Co(CNO)_6]^{3-}$, $[Ru(CNO)_6]^{4-}$, and $[Hg(CNO)_4]^{2-}$. A mixed cyano-fulminato-complex, $Na_4[Fe(CN)_5CNO]$, is obtained from pentacyano-ammino- or pentacyanoaquoferrate(II)- and alkali fulminate. Judging from the absorption spectrum of $[Fe(CNO)_6]^{4-}$ in the visible region and from magnetic measurements, the fulminate ion has a strong ligand field which is only slightly less than that of the cyanide ion. The infrared spectra of simple and complex metal fulminates contain the CN stretching vibration of the CNO ligands at 2200–2000 cm^{-1} and the NO stretching vibration at 1200–1050 cm^{-1}. The C–N–O bending vibrations appear at 500–450 cm^{-1}. The C–N stretching frequency in fulminato-complexes appears at higher wave-numbers than that in alkali fulminates. This leads to the conclusion, that the structure M–C≡N–O (M = metal ion) is favored in the complexes. The infrared spectra indicate linear M–C–N–O groupings. Aryl- and alkyl-metal fulminates such as RHgCNO (R = C_6H_5, $CH_3C_6H_4$, or $C_6H_5CH_2$), $(C_6H_5)_2TlCNO$, and $(C_6H_5)_3SiCNO$ have been prepared [2]. Phenylmercury fulminate is obtained from diphenylmercury and mercury fulminate. Arylmercury fulminates can also be prepared by treating mercury fulminate with arylmagnesium bromide. Triphenylsilyl fulminate, which is readily prepared from triphenylchlorosilane and silver fulminate, has a lower C–N frequency than triphenylacetonitrile-*N*-oxide. This lowering of the frequency can be explained by interaction of the π-electrons of the CN bond with the free d-orbitals of the silicon atom.

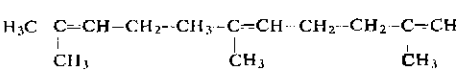
[GDCh-Ortsverband Nordbayern, Erlangen (Germany), June 20th, 1963] [VB 733/102 IE]

German version: Angew. Chem. *75*, 872 (1963)

[1] Cf. *W. Beck* and *E. Schuierer*, Chim. Ber. *95*, 3048 (1962).
[2] Investigations with *E. Schuierer*.

SELECTED ABSTRACTS

The sex attractant of the male bumble bee is farnesol *(1)*, according to *G. Stein*. Substance *(1)* arises in the mandibulary glands and can be extracted with pentane from the heads of male bumble bees. The heads of worker bees contain only traces of *(1)*; extracts of the bodies of males and of workers do not contain any. Compound *(1)* was isolated by chroma-



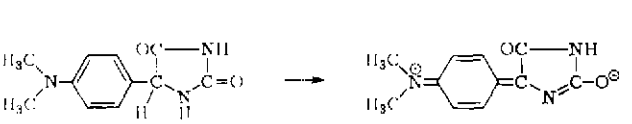
(1)

tography and investigated by ultraviolet and infrared spectroscopy. The physical characteristics are in complete agreement with those of farnesol. The drone presumably takes in the farnesol in his diet as it occurs in almost all flower oils. / Naturwissenschaften *50*, 305 (1963) / –Kr. [Rd 609/180 IE]

Mass spectroscopy of non-volatile substances with molecular weights of up to 800 was achieved for the first time by *C. Djerassi* and co-workers by vaporizing the sample in the electron-stream of the mass-spectrometer. Direct introduction of the sample into the ionization chamber without releasing the vacuum of the spectrometer is achieved using an attachment which is in the form of an introductory system made of glass and which can be evacuated. Dimeric indole alkaloids, porphyrins, and steroid antibiotics were investigated, and the structure of cephalosporin was verified. / Experientia *19*, 211 (1963) / – Re. [Rd 615/174 IE]

Pyridinepolycarboxylic acids and picolinecarboxylic acids have been separated on paper chromatograms by *F. Kuffner* and *F. Schindler*. The separation is valuable for the determination of the structure of heterocycles, especially alkaloids. 2-Butanol/cineol/hydrochloric acid (1:1:1) proved to be a good solvent system. The R_F-values of 28 pyridinecarboxylic acids are given. The spots on the chromatograms were made visible with a new reagent which contains silver acetate, acetic acid, and hydrazine. The limit of detection lies at less than 1 μg. / Mh. Chem. *94*, 252 (1963) / –Re. [Rd 613/184 IE]

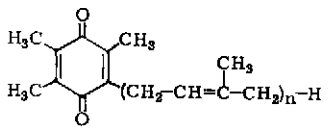
Quinonoid hydantoin dyestuffs were synthetized by *Richard Kuhn* and *W. Blau* as models for a bacterial pigment which probably contains a hydantoin residue. 5-(*p*-Dimethylaminophenyl)hydantoin *(1)* can be dehydrogenated with PbO_2 in acetonitrile/pyridine to give a red, crystalline dyestuff *(2)*



(1) (2)

which decomposes above 150 °C. Dehydrogenation of 5-(3,4-dihydroxyphenyl)hydantoin also yields a red dyestuff as crystals which become dark above 250 °C without melting. / Liebigs Ann. Chem. *662*, 67 (1963) / –Kr. [Rd 607/173 IE]

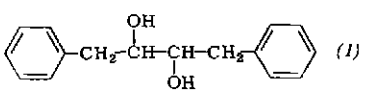
The metabolism of α-tocopherol in the animal body has been investigated by *C. Martius* and *E. Fürer* with the aid of ^{14}C- and ^{3}H-labelled compounds. 2,5,6-Trimethyl-3-(farnesyl-farnesyl-geranyl-geranyl)-1,4-benzoquinone ["$E_{2(50)}$", *(1)*] was identified as the end-product of a series of metabolites. Experiments with trimethylbenzoquinones with various side-chains invariably led to *(1)*, which lends support to a reaction scheme presented for the conversion of vitamin E → $E_{2(50)}$ involving oxidative shortening of the side-chain by 15 carbon atoms and employment of the residue for the construction of



(1), n = 10

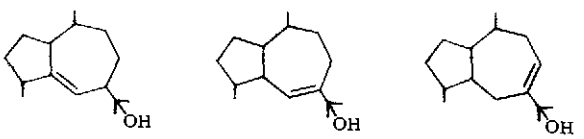
the side-chain of *(1)*. It is assumed that the specific vitamin activity is due to *(1)* and has nothing at all to do with the familiar antioxidant activity of tocopherol. It is of interest to note that the conversion was observed not only in vertebrates (*e.g.* fowl), but also in invertebrates (*e.g.* earthworms). / Biochem. *336*, 474 (1963) / –De. [Rd 612/183 IE]

(+)-1,4-Diphenylbutane-2,3-diol, a new, naturally occurring glycol, has been isolated by *R. Neher* from the testicular tissue of bulls (1.5 g from 2000 kg of tissue). Its structure was elucidated and its configuration confirmed by synthesis. The new glycol, *(1)*, $C_{16}H_{18}O_2$, m.p. 146–147 °C, $[\alpha]_D = +4.6 \pm$ 0.9° in chloroform, c = 1.0957, was synthetized from 1,4-diphenyl-1,3-butadiene by reduction with sodium to yield the 2-butene, oxidation of which with $KMnO_4$ gave the racemic diol (m.p. 123–126 °C). The latter was resolved into (–)-*(1)* and (+)-*(1)* *via* the hemidiphthalate with (–)-cinchonidine. The new glycol was identified as the (+)-compound; it has no oestrogenic or androgenic properties. / Helv. chim. Acta *46*, 1083 (1963) / –De. [Rd 611/182 IE]



(1)

Galbanol, a sesquiterpene alcohol capable of forming an azulene, has been isolated by *M. Wichtle* from galbanum, the latex from several *Ferula* species. Galbanol *(1)*, $C_{15}H_{26}O$, b.p. 142 °C/9 mm, $d^{20} = 0.9466$, $n_D^{20} = 1.4921$, $[\alpha]_D^{20} = +2°50'$ (c = 26.8 in acetone), was isolated from the less steam-volatile fraction of the etheral oil by chromatography on Al_2O_3 with benzene and thin-layer chromatography on kieselgel with benzene/chloroform. It was characterized by its infrared spectrum, molar refraction, dehydrogenation, hydrogenation, and dehydration as an azulenogenic tertiary bicyclic sesquiterpene alcohol. It is isomeric with guaiol and



(1a) *(1b)* *(1c)*

bulnesol and has the formula *(1a)*, *(1b)*, or *(1c)*. On dehydrogenation with sulfur, *(1)* gives predominantly guaiazulene; on dehydrogenation with selenium, guaiazulene and isoguaiazulene are obtained (*ca.* 1:1). / Planta med. *11*, 53 (1963) / –De. [Rd 610/181 IE]

BOOK REVIEWS

Thin-Layer Chromatography by *K. Randerath*, English Edition, translated by *D. D. Libman*. Verlag Chemie G.m.b.H., Weinheim/ Bergstr., and Academic Press, New York and London. 1963. XIV+250 pp., with 79 figures, 5 colored illustrations and 77 tables. Clothbound DM 32.00 = $ 8.00.

Thin-layer chromatography, which was developed by *E. Stahl* just a few years ago, enables several minute samples of mixtures to be separated simultaneously on an adsorbent that has been spread out into a thin layer, and the separated components to be identified by color reactions and R_F values as in paper chromatography. This technique makes all the advantages of adsorption chromatography (rapidity, specific separations, applicability to lipophilic materials) available in the analytical field. It is therefore hardly surprising that thin-layer chromatography has rapidly achieved popularity and that there is already an extensive body of data illustrating the usefulness of the method.

The first section of the present monograph gives comprehensive descriptions of the procedure and equipment, data on adsorbents, choice of solvents, methods of detection, qualitative and quantitative evaluation of the zones of the chromatogram, the use of radioactive isotopes, thin-layer electrophoresis, and recording of chromatograms.

The second section, on special applications, indicates the range of application of thin-layer chromatography (*e.g.* to natural products, drugs, dyes, etc.) by means of examples. One chapter is devoted to the separation of inorganic ions.

The clear, concise text, illustrated by numerous figures and tables, takes up only 250 pages. Both the price and the convenience of the volume have benefited by this sensible compression. This small book will soon be indispensible to all chemists, biologists, and pharmacists who use chromatography and will also help to open up further applications of thin-layer chromatography. *H. Brockmann* [NB 73/59 IE]

Kunststoffe, Struktur, physikalisches Verhalten und Prüfung (Plastics, Structure, Physical Properties and Testing) (in two volumes), edited by the late *R. Nitsche* and *K. A. Wolf*, in collaboration with numerous specialists. Vol. I: Structure and Physical Properties of Plastics (Vol. 6 of the series: Chemistry, Physics, and Technology of Plastics in individual presentations) edited by *K. A. Wolf*. Vol. II: Practical Testing of Plastics. (Vol. 7 of the Series: Chemistry, Physics, and Technology of Plastics in individual presentations), edited by *R. Nitsche*, concluded by *P. Nowak*. Springer Verlag, Berlin-Göttingen-Heidelberg, 1961/62. 1st Edit. Vol. I; XVI, 974 pp., 582 illustr., linen, DM 168.– (about $42.–); Vol. II: XII, 656 pp., 464 illustr., linen, DM 112.– (about $28.–).

The two volumes treat a field of vital interest and meet an urgent need for information on the structure and molecular state of plastics, as a prerequisite for their testing, which is treated in the second volume. It appears that the editors had difficulties with the authors of individual chapters on the approach to the subject matter. Only in this way can the differences in the various sections be explained, where detailed and brief chapters alternate.

Volume I. After an introductory chapter on the importance of the physical investigation of structure, which should either be more detailed or could be omitted entirely, two chapters are devoted to molecular structure, states, and transitions. The excellent tables on the influence of molecular weight and its distribution on the properties of high polymers deserve special mention, as well as the section on molecular forces, because of their precise and clear presentation. In the section on molecular states, attention is particularly drawn to the instructive schematic drawings, which complement the text excellently.

With regard to the chapter on the physical behavior of polymers and its experimental investigation, it would have been

more desirable to learn here and there about the efficacy of the methods discussed. The contributions in this chapter are very detailed and occasionally somewhat too theoretical for the plastics chemist. The contributions on methods of examination, *e.g.* infrared spectroscopy, X-ray diffraction, electron diffraction, electron microscopy, and nuclear magnetic resonance, are admirable and give the reader an excellent survey. The rheology of high polymers as well as the thermal properties could be given somewhat more attention in a new edition.

The section on the physical behavior of combined polymer systems is of interest for both the pure scientist and the practitioner, since the data communicated here are of the utmost importance for the correct application of plastics. The book closes with a chapter on the modification of properties brought about by changes in structure, phenomena which are of great interest to the plastics processer and user. This in particular would make a later enlargement of this section of the book very desirable. The index could also be enlarged by reference to the materials themselves such as polystyrene, polyvinyl acetate, *etc.*; this would help to make the book a popular, practicable work of reference.

Volume II. The practical testing methods are collected in this volume into a good, complete and unified presentation which at present cannot be bettered. The six chapters: Testing Laboratory, Test Samples, Determination of Plastics' Properties, Works and Acceptance Tests of Plastic Products, Evaluation of Results, and Standardization and Quality Control enable those interested in testing and evaluation of plastics to inform themselves rapidly on the best methods, particularly since adequate literature references are attached to each chapter.

It should be emphasized that the editors were able to secure the collaboration of outstanding scientists for their book. For this reason it is bound to find a wide circle of readers among those interested in the physics of plastics, to whom it will be of great value for further study. The appearance of this book is to be welcomed, the editors are to be thanked for their exacting labor and the publishers for the excellent production.

O. Horn [NB 25/53 IE]

Lehrbuch der organischen Chemie (Textbook of Organic Chemistry) by *A. F. Holleman* and *F. Richter*. Walter De Gruyter & Co., Berlin 1961. 37th–41st Edit. XII, 664 pp., 114 illustrations, bound. DM 28.– (about $7.–).

The 41st edition of a textbook which has been appearing since 1898 needs no introduction. It has undoubtedly proved its value, but in view of the drastic changes which organic chemistry has undergone one will tend to read the book with a little scepticism. If one is in favor of the strict adherence to the system used of introducing the subject matter according to the various classes of compounds, then the overall impression is very satisfactory. One finds nearly everywhere examples of substances and reactions that are sensibly chosen for the teacher. Completely new results are also incorporated, *e.g.* the formulation of Grignard compounds, ozonisation products, the diazonium-diazotate equilibrium, and biological syntheses of fatty acids, isoprenes, *etc.*, and most of the original literature is referred to.

Already in the foreword to the first edition, *A. Holleman* wrote: "Physico-chemical theories are introduced in suitable places, for example, on the laws of esterification, ionisation, *etc.*" *F. Richter* has consistently developed this theoretical approach in the new editions. Thus, chemical bonding at saturated and unsaturated carbon atoms and in benzene is fully discussed. The R and S nomenclature and conformation in stereochemistry are dealt with. The derivation of the laws of dissociation of polybasic acids and of amino acids at the isoelectric point is described, and even the Hammet equation and *Kuhn*'s theory of color are mentioned. The significance of absorption spectra is explained with several examples; an infrared spectrum is also shown. Comments on these aspects are naturally found dispersed throughout the book, as their chief significance concerns the characterization of substances and reactions, but there are also intelligently incorporated characteristic reaction schemes (*e.g.* of the Wagner-Meerwein rearrangement, aromatic substitution, *etc.*). The constant revision of the book has obviously necessitated the frequent use of passages in small type, in which the somewhat condensed text is more difficult to read. Sometimes, also, precise structural formulae would be desirable (terpenes!), although with few exceptions (quaternary salts of quinoline and cyanine, p. 543), obsolete formulae have been eradicated. The 8-page supplement on current research (placed at the end for lack of space) proves to be of little value, as continuity with the main text is not established. The concluding chapter on nomenclature and on the most important chemical literature is very welcome.

On the whole, the late author *F. Richter* has certainly succeeded well in uniformly modernizing Holleman's work while maintaining its original conception.

S. Hünig [NB 15/47 IE]

Encyclopedia of Plant Physiology, edited by *W. Ruhland*. Vol. IX: The Metabolism of Compounds Containing Sulfur and Phosphorus. Subeditor: *P. Schwarze*. Springer-Verlag, Berlin-Göttingen-Heidelberg 1958. 1st edit., X, 306 pp., 30 Figs., clothbound, DM 88.– (about $ 22.–).

The present volume of the well-known, large encyclopedia has as its object a comprehensive treatment of the metabolism of compounds containing sulfur and phosphorus, although – in accordance with relationships to the overall metabolism – numerous individual findings concerning substances of these classes are also referred to in other volumes of the encyclopedia. To avoid too extensive repetitions, fields which are already discussed in detail in other volumes were dealt with quite summarily in this volume; nucleic acids as well as amino acids containing sulfur and proteins containing these are not even discussed at all here, because these classes of substances have already received detailed treatment in Vol. VIII, which is devoted to the metabolism of nitrogen compounds.

The individual contributions, eleven of which are in English, five in German, and two in French, have all well-known experts in the appropriate fields as authors. They provide a good survey of the state of knowledge at the time of completion of the article, *i.e.* around 1957. It is understandable that since then substantial new knowledge in all of the fields dealt with has accrued. Nevertheless, there is no doubt that even today all biochemists and plant physiologists occupied with the problems discussed in the present volume will be able to make profitable use of the ample material presented here. The detailed subject index is also of special value.

The research worker will, of course, only get the full use from a volume such as that reviewed here, if he has the complete work at his disposal.

O. Hoffmann-Ostenhof [NB 69/58 IE]

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A Secret of Chinese Porcelain Manufacture

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The secret of old Chinese porcelain is the technique by which a material, capable of forming extremely thin-walled articles, was obtained from a slightly plastic kaolin. Intercalation compounds, which form by treating kaolinite with decaying urine, give the key to the preparation of this material.

Porcelain has been made in China probably since the 6th or 7th century A. D. Quartz, felspar, and kaolin were then, as now, the raw materials employed. The name "kaolin", for china clay is probably derived from old deposits on the mountain Kao-ling in China. Today, however, it is not at all certain whether it was kaolin or felspar or a kaolin-felspar mixture that was actually mined from the Kao-ling deposits. They were already exhausted when the geographer *Richthofen* examined them between 1868 and 1872 [1].

Prolific exports of porcelain from China to Japan, Korea, and the Arabian countries took place as early as the 9th century, as shown for instance by the procelain fragments found in excavations at Samarra on the Tigris and the many funerary wares preserved in Japan [2]. In the 16th and 17th centurics, quantities that must be regarded as enormous for that time were brought to Europe. The passion for collecting Chinese and Japanese porcelain had assumed the proportions of a malady, according to Augustus the Strong (King of Poland, Elector of Saxony, 1670–1733), who was himself one of the principal collectors of his time [*]. The connoisseurs were particularly charmed by the artistic appearance, the pleasing forms, the varied decorative treatment, the accomplished painting, and the wealth of motifs, which offered insight into the mythology and symbolism of the Chinese.

In the 9th century, it was already known that this pottery had extremely thin shards. *Kahle* [3] reports the wonderment of a Mohammedan trader in 851 A.D.: "The Chinese have a particularly fine clay which they use to make drinking vessels with the delicacy of glass; the sparkle of water can be seen in them although they are made of clay." Articles made of Chinese porcelain of great strength, shaped perfectly by hand, and having a wall thickness of less than 0.4 mm are known.

The technical side, unlike the artistic aspect of ancient Chinese porcelain, still harbors its secrets today. There is a host of results available from investigations into processes of the 19th century, obtained principally by the porcelain factories at Sévres [4–6]. However, first-hand reports on the raw materials and techniques of earlier periods [7], *e.g.* the two letters of the Jesuit Father *d'Entrecolles* [8], the report of *T'ang Ying* (1682–1754) the Director of the Imperial Porcelain Factories at Ching-tê-Chên [9], the "Description of the Ceramic Art" (Tao Shuo) in six volumes by *Chou Yen* (1774) [10], or the other original Chinese texts translated and edited by *St. Julien* [5], are vague on chemical questions. The omissions become particularly obvious when the development of extremely thin-walled porcelains (such as the delicate South Ting ware) is considered. The art of its manufacture is said to have been highly developed in the second half of the Sung period (960–1279), but was lost

[*] The Jesuit Father *d'Entrecolles* [8] reported in his letters (1711–1722) that there was a population of more than a million in the great porcelain centre of Ching-Tê-Chên and that about 180000 families were engaged in pottery. Over 3000 furnaces operated day and night. The harbor was about a mile long and ships would at times lie two and three deep along the quay. Articles were mass-produced and each passed through about sixty hands before completion.

[1] *E. Zimmermann:* Chinesisches Porzellan. Seine Geschichte Kunst und Technik. 1913; *B. Laufer:* Beginnings of Porcelain in China. Chicago 1917.

[2] *F. Sarre:* Die Keramik von Samarra. Berlin 1925.

[3] *P. Kahle*, Z. dtsch. morgenland. Ges. *13*, 10 (1934); Trans. oriantal ceram. Soc. (London) *1940/41*, 27.

[4] *I. I. Ebelmen* and *A. Salvetat*, Ann. Chim. Physique, 3e Ser. *31*, 257 (1852).

[5] *M. S. Julien*, Histoire et fabrication de la porcelaine chinoise; ouvrage traduit du chinois, accompagne de notes et d'additions par A. Salvetat. Paris 1856.

[6] *G. Vogt*, Bull. Soc. d'Encouragement pour l'Industrie nationale, 5e Ser. *5*, 530 (1900).

[7] Compilation of the older Chinese literature: *P. David*, Trans. oriental ceram. Soc. (London) *1936/37*, 20.

[8] *Pere d'Entrecolles:* Lettres édifients et curieuse, écrites des Missions étrangères. Paris, *12*, 253 (1717); *19*, 173 (1781); New Edition: Noel Etienne Sens. Paris 1810.

[9] *Meng-Chang-Ling*, Bull. Amer. ceram. Soc. *19*, 29 (1940).

[10] *Shu Yen:* T'ao Shuo (Description of Ceramic Art), 1774, 6 volumes. Extracts given by *M. S. Julien* [5].

under the Mongol domination during the Yuan dynasty (1280–1368). The ancient art was recalled during the following Ming period (1368–1643), but porcelain manufacture of this thin-walled type was at first no longer succeessful. Even the most plastic kaolin of the period from the deposits of Sing-chêng-tu in the Matsung mountains, which was monopolized by the Imperial Factories and was therefore designated as "government clay" (Kuan-T'u) gave results that were very unsatisfactory. Imitation of egg-shell porcelain (t'o t'ai = bodyless procelain) was finally achieved only towards the end of the Ming period or the beginning of the Ching dynasty (1644–1722). In this process, another plastic substance, called Hua shih, a plastic illite or illite-rich clay that turns white with a greenish cast on firing, was probably used instead of kaolin [*]. With this clay, it was again possible to produce egg-shell porcelain and open, reticulated patterns. These ornaments were called Ling-lung or Kuei-Kung (devil's work), to indicate that they transcended human skill. They had to be produced at the order of the Emperor, in spite of the protests of the potters [11]. The higher dry strength of the illitic clays permitted the walls of the formed and dried articles to be scraped thinner with steel blades. Although the technical imitation was thus wellnigh successful and even surpassed the bluish-white (snow-white) originals with its warmer white (blanc de chine) tones, it still left the ancient technique a mystery until today. Investigations already undertaken during the early Ming period indicated that a kaolin of only poor plasticity and not illite, was used for the original egg-shell porcelain. This aspect of ceramic art was therefore regarded as mysterious even as early as 1500. Investigations on rejected, misfired shards of the particularly delicate Ting porcelain of the South-Sung period suggested the probability, that a quite coarsely crystalline kaolinite was actually used, which corresponds approximately to that of the Amberg-Hirschau basin in Germany.

All previous experience has indicated, that these coarsely crystalline clays have very poor plasticity. Their dry strength is also low.

The secret of the ancient Chinese porcelain must therefore ultimately lie in some technique enabling articles to be formed from kaolin of poor plasticity, which would normally be expected to require clays of extremely good plasticity and high dry strength.

Porcelain was considered particularly valuable by the Chinese and its symbol in Chinese writing was the same as that for peace; – both being precious and requiring great care. The most exquisite pieces were reserved for the Imperial Court [**]. In consideration of this high esteem, it is remarkable that the hand craft should come to be lost.

The results given in Table 1 show [6, 12] that the composition of the porcelains remained practically unaltered for more than two centuries, although analytical methods were then unknown. It must therefore have depended entirely on the tactile sensitivity of the ceramics craftsmen. It is possible that the evacuations and dislocations caused by the Mongolian invasion (1279), the preference for boldly colored porcelain, which became fashionable under the Mongolian rule, the greatly expanded mass production demanded by the increased export trade, and the emigration of noted ceramic craftsmen to Indochina, Annam, and Siam [11] all contributed to the loss of the secret procedures. Alternatively, this particular art may well have been a family secret, such as the *Ho* family possessed for the production of vases with a moireed copper red glaze, which could not be uncovered in spite of the most sophisticated industrial espionage. Espionage was indeed common, as is shown by the strict control and the threat of dire penalties for the misappropriation of the raw materials used in the production of Mohammedan Blue or Hui-ching (dark, blue-black), from the Imperial factory at Chin-tê-chên [5].

Table 1. Composition of Chinese porcelains from different periods. The figures indicate percentages by weight in the clay ready for working.

	about 1710 [a]	1850 [b]	1890 [c]
SiO_2	69.51	69.00	69.50
Al_2O_3	22.72	23.60	23.10
Fe_2O_3	1.84	1.20	2.00
CaO	0.27	0.30	0.16
MgO	0.36	0.20	0.22
K_2O	4.79	3.30	3.72
Na_2O	0.87	2.90	1.28
Σ	100.36	100.5	99.98

[a] Vase celadon green glaze ("old Chinese" clay) [13].

[b] Analyses from [3].

[c] From the French Consul in Hankow; clay supplied to the porcelain factory at Sèvres.

The Chinese generally used more kaolin in their porcelain mixtures than the Europeans in later years. The firing temperature was about 100–200 °C lower, not because the body could not tolerate a higher temperature but because of the glaces. These were applied to the air-dried article, and the porcelain was complete in a single firing [14]. With our ceramics, on the other hand, the glaze is applied to the fired biscuit and the article is completed in a second firing.

A last distinction was the pretreatment of the kaolin. The Chinese subjected it to an ageing process, which is said to have consisted of slurrying the kaolin with urine in large pits and storing it there before final processing. Reports on the duration of this treatment are contradictory and vary from short periods to a hundred years and more [14].

Frequent attempts have been made to relate the delicacy of Chinese porcelain to changes in the clays during ageing but without finding a really satisfactory explanation. Before the possible modes of reactions can be discussed, it will be advantageous to examine the structure of kaolin more closely.

[*] Hua-shi (slippery stone) is frequently interpreted as soapstone (steatite); however, its chemical composition, particularly its high alkali content, point to illite or an illite-rich clay.

[11] *W. B. Honey:* The Ceramic Art of China, London 1944.

[**] One particularly valuable old vase has as emblem, the symbol of the house of *Liu-Kuei-fei* († 1187), the concubine of the South Sung Emperor *Kao-Tsung* [7].

[12] *W. Funk*, Naturwissenschaften *29*, 18 (1941).

[13] *A. B. Meyer:* Altes Seladonporzellan. Berlin 1885; *H. Hechi*, Tonind.-Ztg. *14*, 637 (1890).

[14] *W. Funk*, Ber. dtsch. keram. Ges. *22*, 163, 205 (1941); *23*, 187, 326 (1942).

I. Structure of Kaolinite

Kaolin (china clay) is the term applied to a mixture of minerals containing small amounts of quartz and illite with a preponderance – up to 99 % in good kaolins – of the clay mineral kaolinite $Al_4(OH)_8Si_4O_{10}$. Kaolinite consists of individual layers in which the silicon atoms are tetrahedrally surrounded by oxygen atoms (Fig. 1). Adjacent tetrahedra are linked together by a common oxygen atom to form a two-dimensional layer lattice. Of the four oxygen atoms in each tetrahedron, only three lie in the plane in which they can participate

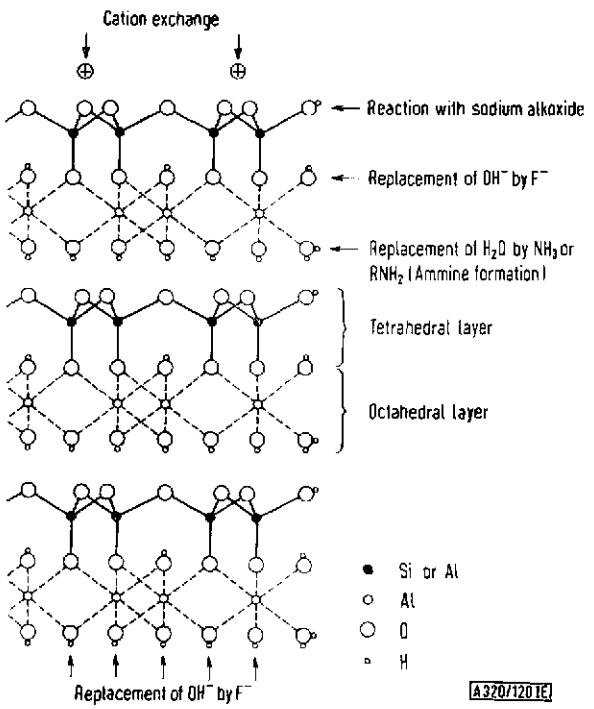


Fig. 1. Reactive sites on the surface of a kaolinite crystal.

as ligands. The fourth is situated below this plane and simultaneously belongs to an octahedron of oxygen and hydroxyl ions, the centre of which is occupied by an aluminum atom. Each octahedron has an edge in common with three others (*i.e.* two OH^--ions or one O^{2-} -and one OH^--ion [15].

These two-dimensional infinite layers are chemically very stable. They are not attacked appreciably by dilute acids or alkalies. Chemical changes in the ageing pits must therefore by restricted to the crystal surfaces. The reagents available in decaying urine are ammonium ions, ammonia, urea, and hydroxyl ions.

II. Chemical Reactions on the Surfaces of Kaolinite Crystals

The reactive centres on the surface of a kaolinite crystal are indicated in Figure 1. All noteworthy effects on the kaolinite surface have in the past been ascribed to broken bonds, which are said to occur in large numbers on the crystal boundary, where the Si–O–Si bonds that exist within the body of the crystal can no longer be formed.

Ionic (≡Si–O^- and $^+$Si≡) or radical (⩾Si–O· and ·Si≡) groups capable of effecting ion exchange or oxidation [16] are supposed to be present on these fracture planes. Today we know that such groups occur only when the dry kaolinite is ground. If grinding is carried out in the presence of aromatic amines, these are rapidly oxidized. The broken bonds heal out quickly in aqueous solution with the formation of ⩾Si–OH groups and oxidation does not take place. For this reason, broken bonds probably do not play an important part in influencing the plastic properties.

The ⩾Si–OH groups on the surface of kaolinite crystals display all the reactions known from low molecular-weight silicon compounds. Under anhydrous conditions, they are converted into ⩾Si–Cl compounds, which are alkylated by Grignard reagents, and they react with alkoxides to give silicic esters. In strongly alkaline medium, they form alkali salts and can thus also nominally participate in cation exchange. However, the salts formed are hydrolysed even at pH 10, so that their contribution to the properties of ceramic clays is negligible, if alkaline casting slips [*] are omitted from this consideration. This technique was unknown to the Chinese.

Complex formation is restricted to the aluminum atoms lying at the boundaries of the octahedral layer. These are able to accept H_2O or other polar molecules such as NH_3 or alkylamines to complete their octahedral coordination. These complexes, however, decompose in aqueous suspension to reform the aquo complexes.

Cation exchange is more important for the properties of ceramics. The cations have considerable influence on the viscosity, thixotropy, plasticity, and dry strength of kaolins (Table 2) [17].

Table 2. Influence of exchangable cations on the ceramic and rheological properties of Zettlitz kaolin.

Exchangable cations	Water content of the thixotropic system gelling within 6 sec. [ml/3 g of kaolin]	Bingham yield limit [dyne/cm²]	Plasticity acc. to *Pfefferkorn* [a] [g of H_2O/100 g of kaolin]	Dry bending strength [kg/cm²]
Na^+	3	50	43.5	30
K^+	3		45	22.4
Ca^{2+}	8	300	46.5	16.3
Ba^{2+}	8	440	47.3	10.2
La^{3+}	7	580	50.6	8.4
($H_3O^+ + Al^{3+}$)	12.5	850	52	13.7

[a] Compression from 40 to 16 mm.

[15] *I. W. Gruner*, Z. Kristallogr., Mineralog. Petrogr., Abt. A, *83*, 75 (1932).

[16] *P. Marshall Jr.*, Kolloid-Z. *119*, 53 (1950); *W. Eyl*, ibid. *119*, 53 (1950); *E. A. Hauser, D. S. Le Beau*, and *P. P. Pevear*, ibid. *119*, 53 (1950).

[*] The slip-casting process consists in pouring a suspension of suitable composition and concentration into an preshaped plaster mould, the highly porous nature of which removes water from the slip mainly by capillary action. In the neighborhood of the plaster wall the suspension becomes locally concentrated and a type of skin formation develops. The longer the slip is left in the mould, the more water is removed and the skin or compacted layer becomes thicker. The process can be stopped at any time oby puring off the excess liquid.

[17] *U. Hofmann, E. Scharrer, W. Czerch, K. Frühauf*, and *W. Burck*, Ber. dtsch. keram. Ges. *39*, 125 (1962).

The distribution of exchangable cations is not homogeneous over the surface of the kaolinite crystal. They are situated almost exclusively on the Si–O surface where they are bound by aluminum atoms that are located there by interchange of their normal lattice sites with approximately every second silicon atom. The quantity of the exchangable cations therefore depends only on the thickness and not on the diameter of the crystallites [18].

The exchangable ions bound in natural and slurried kaolins are mainly Ca^{2+}, and in the production of casting slip, the latter are largely replaced by Na^+-ions [19].

$$Ca(\text{Kaolinite})_2 + Na_2CO_3 \rightleftharpoons 2\,Na(\text{Kaolinite}) + CaCO_3$$

Partial substitution of Ca^{2+}-ions by NH_4^+ does take place during ageing but does not influence the behavior beyond the limits set by Ca^{2+}, Na^+, and K^+.

Exchangable anions are bound on the edges of the crystallites (prismatic planes). As far as could be ascertained up to the present, only phosphate and polyphosphate anions influence the rheological behavior [20], but the effect is less marked than that of the cations.

Prolific growth of micro-organisms is also to be expected in the decaying urine in the ageing pits. Their secretions and decomposition products appear to improve the plastic qualities of the clay slightly [21]. This improvement probably depends upon interaction of organic polyelectrolytes and polyhydroxy compounds with the surface of the clay.

III. Reactions within Kaolinite Crystals — Intercalation Compounds

A single kaolinite layer can be considered as a two-dimensional infinite macromolecule. These macromolecules are crosslinked by hydrogen bonds Al–OH···O–Si to the three-dimensional crystal lattices. It is known from protein chemistry that hydrogen bonds between macromolecules can be broken by certain low molecular-weight substances, such as urea or formamide. It was therefore essential to test the behavior of kaolinite in concentrated solutions of urea or formamide. Quite surprisingly, complete reaction took place [22]. The kaolinite crystals did not dissolve, but the urea molecules penetrated into the crystal lattice and increased the distance between the kaolinite layers from 7.2 to 10.7 Å. An intercalation compound was thus formed, from which the urea could be recovered quantitatively by leaching with water. An intermediate stage with a basal plane spacing of 8.3 Å can be achieved by means of careful and incomplete washing. However, this is only a statistical mean distance and appears to depend on the diameter of the kaolinite crystallites.

[18] *A. Weiss*, Z. anorg. allg. Chem. *299*, 92 (1959).

[19] *W. Czerch, K. Frühauf*, and *U. Hofmann*, Ber. dtsch. keram. Ges. *37*, 255 (1960).

[20] *H. van Olphen*, Clays and Clay Minerals *7*, 421 (1958).

[21] *F. Oberlies*, Naturwissenschaften *45*, 487, 513 (1958); *E. C. Stover*, Trans. Amer. ceram. Soc. *4*, 183 (1902); *5*, 358 (1903); *G. Pohlmann* and *F. Oberlies*, Naturwissenschaften *47*, 58 (1960); *D. P. Glick*, J. Amer. ceram. Soc. *19*, 169, 209, 240 (1936); *Komuro-Hideo*, J. Koyoto Women's Univ. *1*, 1 (1952).

[22] *A. Weiss*, Angew. Chem. *73*, 736 (1961).

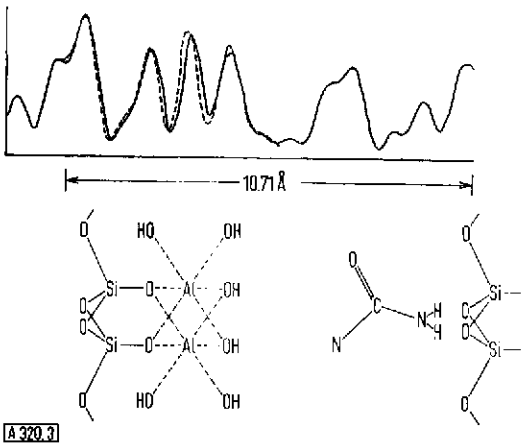
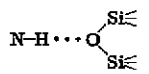


Fig. 2. One-dimensional electron density projection of urea-kaolinite normal to the layer.
—— Electron density in urea-kaolinite.
- - - Electron density in pure kaolinite.

The arrangement of the urea molecules relative to the silicate layers [23] was determined by a one-dimensional electron density projection.

The length of the hydrogen bond



is 2.81 Å at the maximum, *i.e.* the urea molecules also form strong hydrogen bonds with the kaolinite layers (Fig. 2). Formamide, acetamide, or hydrazine react like urea. The reaction rate at 20 °C decreases strongly in the order: 35% aqueous hydrazine > saturated aqueous urea > formamide > acetamide (Fig. 3).

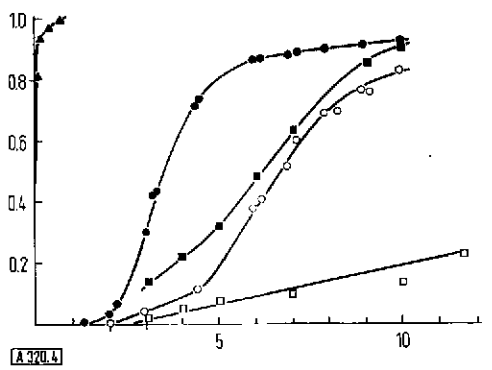


Fig. 3. Rate of intercalation of urea, formamide, and hydrazine in kaolinite (Schnaittenbach Kaolin OF).
Ordinate: Extent of reaction.
Abscissa: Reaction time [days].
□ Intercalation of urea from a saturated aqueous solution at 20 °C;
■ Intercalation of urea from a saturated aqueous solution at 65 °C;
○ Intercalation of formamide from a 12 M solution in ethanol/H_2O (1:1 v/v) at 25 °C;
● Intercalation of formamide from pure, liquid formamide at 25 °C;
▲ Intercalation of hydrazine from a 10.9 M aqueous solution at 2 °C.

Kaolin can also react with compounds incapable of forming hydrogen bonds. This was first observed by *Wada* in 1961 during experiments with saturated solutions of potassium acetate. Potassium acetate "molecules" also penetrate into the body of the kaolinite

[23] *A. Weiss, W. Thielepape, G. Göring, W. Ritter*, and *H. Schäfer* in: International Clay Conference 1963. Pergamon Press, London, 1963.

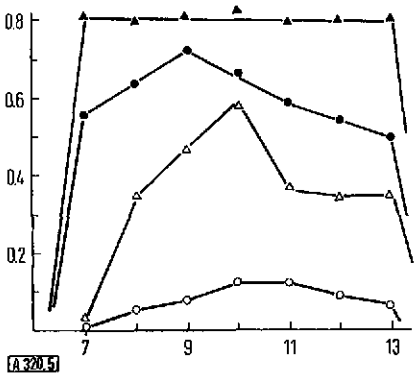


Fig. 4. Dependence on pH of the intercalation in kaolin (Schnaittenbach) of potassium acetate from a saturated aqueous solution.
Ordinate: Intensity ratio $I_{14.0}/(I_{14.0} + I_{7.2})$ [*].
Abscissa: pH value.
O—O 3 hours at 0 °C; ● ● 24 hours at 0 °C;
△—△ 3 hours at 40 °C; ▲—▲ 24 hours at 40 °C.

crystal lattice between the layers and increase the basal plane spacing by about 7 Å to a final value of 14·2 Å [24].

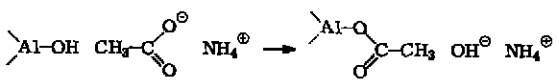
The reaction is strongly dependent upon the pH (Fig. 4) and occurs only in the alkaline region [23]. This would tend to suggest, that the formation of a basic aluminum acetate plays a part in the reaction. The size of the cation is perhaps also decisive, since the reaction proceeds completely only with potassium, rubidium and caesium acetates, but not with sodium, magnesium, calcium, or lithium acetates, [23]. With the propionates, however, the sodium salt does react completely (Table 3). The orientation of the acetate ions has not yet been explained unequivocally. Judging by the large basal plane spacing the anion should stand perpendicular to the kaolinite layer lattice. One-dimensional electron projections onto the normal to the layers give only the precise location of the cations. These are immersed in the six-membered oxygen rings of the silicate layers.

Table 3. Intercalation of alkali salts of low molecular-weight fatty acids from satured aqueous solution at pH 9 into the silicate layers of kaolinite

	Basal plane spacing [Å]	
	in the salt solution	after leaching with water
Lithium acetate	7.2	7.2
Sodium acetate	7.2	7.2
Potassium acetate	14.0	7.2
Rubidium acetate	14.4	7.2
Caesium acetate	14.7	7.2
Sodium propionate	11.1	7.2
Potassium propionate	11.2	7.2
Rubidium propionate	11.2	7.2
Caesium propionate	ca.11.8	7.2

Ammonium acetate also reacts completely. It is formed in copious quantities during bacterial decomposition and fermentation of urine. The formation of ammonium acetate-kaolinite must therefore also be expected during the ageing with urine.

The temperature dependence of the intercalation reaction of ammonium acetate from aqueous solution at pH 9 is particularly remarkable. The rate of reaction has a maximum at 20–30 °C. About 2.5 moles of ammonium acetate per mole of $Al_4(OH)_8Si_4O_{10}$ are bound if the intercalation proceeds quantitatively. At pH 9, in addition to ammonium acetate, some free NH_3 is also intercalated from the ammoniacal solution. On exposure to air, these NH_3 molecules are exchanged with water molecules, and the interlayer distance is thus increased by further 3 Å to a value of 17 Å. The ammonium ions probably leave through the gap above the oxygen hexagons to locations above the oxygen triangles. However, it cannot be excluded that acetate ions may take the places of some OH^--ions during this process.



Different foreign molecules dissolved in the saturated aqueous urea or ammonium acetate solution can also be intercalated between the kaolin layers, although they cannot normally enter the lattice from pure saturated or dilute solutions, for example, n-alkylamines or potassium salts of amino acids (glycine, alanine, lysine).

IV. Are Kaolinite Intercalation Compounds Formed during Ageing?

The results of experiments with pure urea or ammonium acetate showed that intercalation compounds of kaolinite could also be formed during ageing. However, since certain compounds can inhibit the process of intercalation by complex formation, actual tests appeared to be necessary. An accidental observation gave a direct answer and made these experiments unnecessary.

During the author's vacation in the Bavarian Forest in 1961, excavations for a new stable were being made at a neighboring farm. In the clefts between the outcropping coarse-grained granite in the excavation, the author observed a kaolin-like mineral. X-ray investigations showed that this was indeed a pure kaolinite-urea intercalation compound [22]. From enquiries, it appeared that the dung-heap and liquid manure pit of the farm had for decades occupied the site of the excavation. The kaolin had obviously taken up urea from the manure that had percolated through it over the years and formed the intercalation compound. It can therefore now be said with certainty that intercalation reactions take place during ageing.

V. Improvement of the Ceramic Properties of Kaolinite by Processing Intercalation Compounds of Kaolinite

The ancient Chinese art of ageing with urine [25] was formerly also used in Europe and was already known to the Romans. In Germany, urinary ageing was prac-

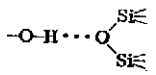
[*] $I_{14.0}$ = Intensity of reflections of (001) planes of potassium acetate intercalation compounds of kaolinite.
$I_{7.2}$ = Intensity of reflections of (002) planes of the same intercalation compound and of (001) planes of unchanged kaolinite crystals.

[24] *K. Wada*, Amer. Mineralogist *46*, 78 (1961).

[25] Quite romantic notions have also been recorded in some quarters; *e.g. G. Panciral* writes in "The Book of Lost Antiquities" (1617): "that the clay is secretly buried in the earth by the head of the household, who transmits his knowledge only to his children. There it lies buried for 80 years without seeing the light of day. When the heirs have unearthed it and found it suitable for working they fashion from it precious translucent vessels." Cf. *M. Beurdeley:* Porzellan aus China, Compagnie des Indes. Bruckmann-Verlag, München 1962.

tised mainly in the late middle ages. However, apparently no appreciable increase in plasticity was achieved by this treatment. It therefore appears reasonable to ask whether ceramic properties can be improved at all with the aid of intercalation compounds of kaolinite.

Nowadays ceramic clays are wet-ground in large ball-mills before processing. The crystal platelets slide against each other during this process and become thinner [26a, b]. With each shift of the layers by one-sixth of the crystallographic b-axis, the layers are again so coordinated that equivalent cross-linking hydrogen bonds can snap into place [27].



Wet-milling is therefore not very effective.

In the intercalation compounds of kaolin, the kaolinite layers are separated by the intercalated molecules and are thus no longer cross-linked through hydrogen bonds. The separating layer in ammonium acetate-kaolinite is as thick as 7 to 10 Å. The bonding forces between the kaolinite layers can therefore be expected to be rendered considerably weaker. Accordingly, it is possible to divide a single crystal [28] of ammonium acetate-kaolinite 1 mm thick into the finest lamina of less than 1 μ thickness without changing the diameter of the platelet appreciably. Grinding of intercalation compounds of kaolinite is therefore likely to be considerably more effective than wet milling of untreated kaolinite. The electron micrographs shown in Figure 5 confirm this quite impressively. The crystallites are much thinner even after only a brief period of milling. It is characteristic that the thinner lamina begin to curl from the

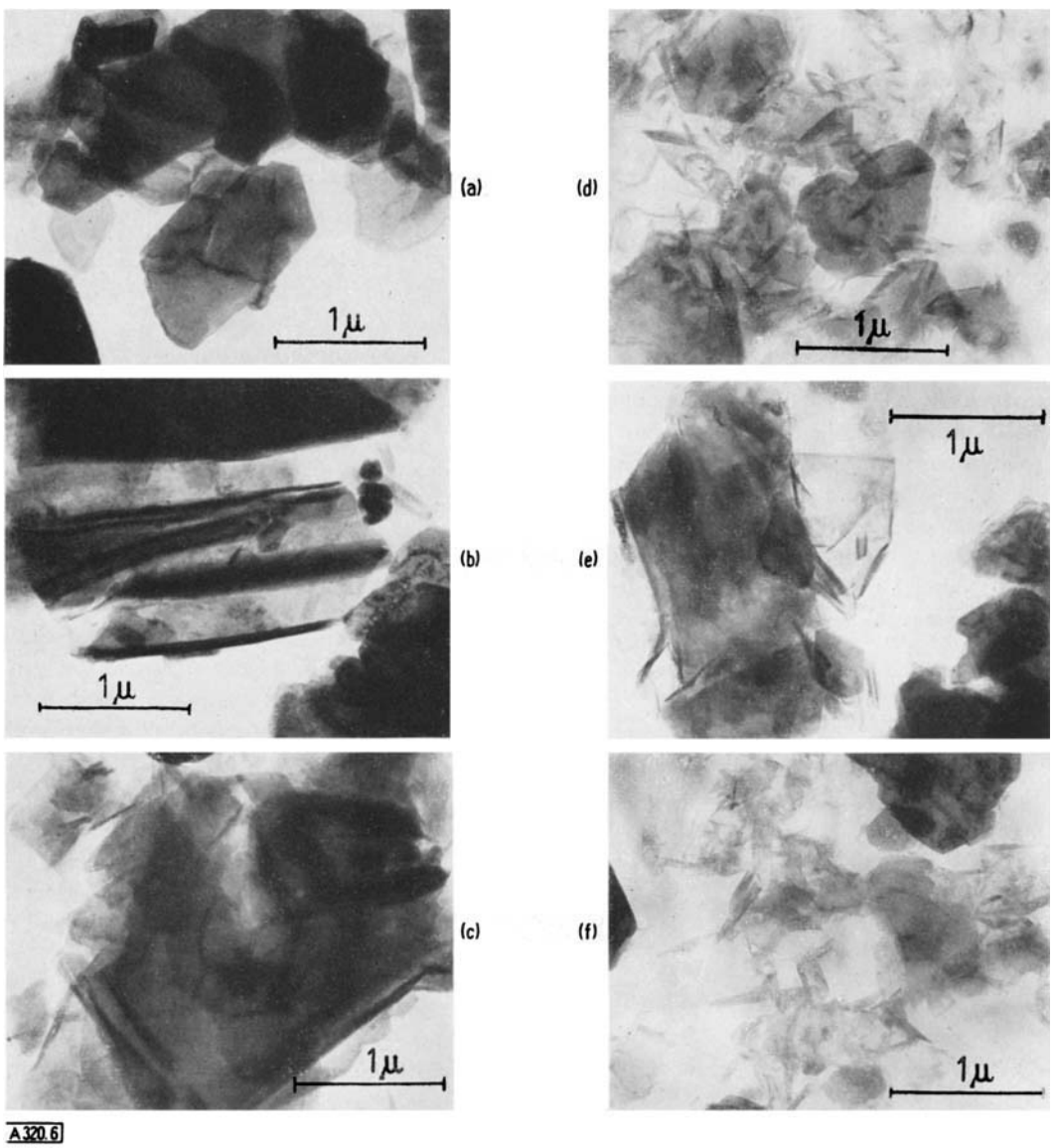


Fig. 5. Electron micrographs of various kaolin samples.
(a) Schnaittenbach kaolin OF.
(b) Ammonium acetate-kaolin ball-milled for 28 hours.
(c) Ammonium acetate-kaolin ball-milled for 128 hours.
(d) Urea-kaolin pulverized for 15 min in a mortar.
(e) Ammonium acetate-kaolin pulverized for 30 min in a mortar.
(f) Ammonium acetate-kaolin pulverized for 15 min between perspex plates.

[26a] *B. T. Shaw*, J. physic. Chem. *46*, 1031 (1942).

[26b] *U. Hofmann* and *E. Scharrer*, Clay Minerals Bull. *2*, 210 (1954).

[27] *G. W. Brindley* and *G. Brown*: X-Ray Identification and Crystal Structures of Clay Minerals. Mineralogical Society, London 1961.

[28] The kaolinite crystals were obtained from the Central Cordillieras (Loceria Columbiana, Medellin, Columbia) and were recently described by *D. Paetsch*, B. dtsch. keram. Ges. in the press.

crystal edges. This confirms the assumption of *Bates*, that the strain in the kaolinite layers due to different dimensions of the octahedron and tetrahedron layers is relieved by this curling. Finally wrinkled aggregates appear which seem to be more characteristic of a bentonite than of a kaolinite.

It must be clarified here that the ball-mill was not known to the Chinese. Hard specimens were crushed in water-powered hammer mills. Aged kaolins were pulverized manually in mortars or stamped and mixed by buffalos. Experiments showed that even brief rubbing of a kaolinite intercalation compound in a mortar or between two glass plates is much more effective than treatment in the ball-mill.

The plasticity of kaolin is higher, the better the kaolinite crystallites are able to cling to and envelop the quartz and felspar grains. Division of single kaolinite crystals into ten, a hundred, or even more thinner flexible platelets by grinding of intercalation compounds of kaolinite can therefore be expected to improve the plasticity of the kaolin enormously.

The thixotropy of the kaolin does indeed increase strongly with this pretreatment. A paper kaolin of low thixotropy subjected to this treatment yields a material surpassing the best ceramic kaolins and approximating activated bentonites (sodium montmorillonites) (Table 4).

Table 4. Alteration of the thixotropic properties of kaolinite with grinding of ammonium acetate-kaolinite.

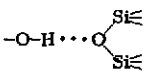
Sample	Water content of the thixotropic system gelling within 6 sec. [ml/3 g of Kaolinite]	
	NH_4^+-kaolinite	Ca^{2+}-kaolinite
Kaolinite OF (Schnaittenbach)	2.1	4.3
Wet-ground for 6 days	3.1	5.8
Ammonium acetate-kaolinite		
Ball-milled for 24 hours	10.6	8.6
Pulverized for 30 min in a mortar	11.0	10.3
Pulverized for 120 min in a mechanical mortar	24.0	22.7
Colloidal kaolin (Chodau)	4.0	7.1
Kaolin (Zettlitz)	3.8	9.0
Montmorillonite (Geisenheim)	36.0	10.2

Table 5. Change in the dry strength of kaolin with grinding of intercalation compounds of kaolinite.

Sample	Dry strength [kg/cm²]
Kaolin OF (Schnaittenbach)	ca. 1.0
Ammonium acetate-kaolinite Pulverized for 30 min in a mortar and leached	ca. 6.0
Pulverized for 15 min between polyethylene plates and leached	ca. 32
Pulverized for 120 min in a mechanical mortar and leached	>46
Urea-kaolinite Pulverized for 15 min between polyethylene plates and then leached	ca. 18
Zettlitz kaolin	16.3
Very fine kaolins	ca. 15
Clays	22
Illite (Sarospatak)	49
Bentonite diluted 1:2 with Schnaittenbach kaolin	86

The dry-strength is important for egg-shell porcelains. Just this property increases beyond expectation with the grinding of intercalation compounds of kaolinite (Table 5) and is particularly well shown on comparison with the best ceramic kaolins and illites.

The firing characteristics and shrinkage are influenced only slightly, but also favorably. The intercalation compounds are only stable in concentrated solutions of the intercalated compounds. The intercalated molecules are eluted quantitatively when water is added as diluent. However, with the consequent collapse of the enlarged basal plane spacing, hydrogen bonds



can no longer be formed as regularly as in the original kaolin. For this reason, the major part of the water is already lost at 400–450 °C from these expanded kaolins and not at 500–550 °C as in the original kaolin (Fig. 6). For this dehydroxylation process, two decomposition stages

$$Al_4(OH)_8Si_4O_{10} \rightarrow Al_4(OH)_2O_3Si_4O_{10} + 3H_2O \quad \text{and}$$
$$Al_4(OH)_2O_3Si_4O_{10} \rightarrow Al_4O_4Si_4O_{10} + H_2O$$

are hinted which are not found with natural kaolin. The considerable shrinkage due to dehydroxylation is here spread over the range 400–550 °C while with untreated kaolinite it occurs between 500 and 550 °C.

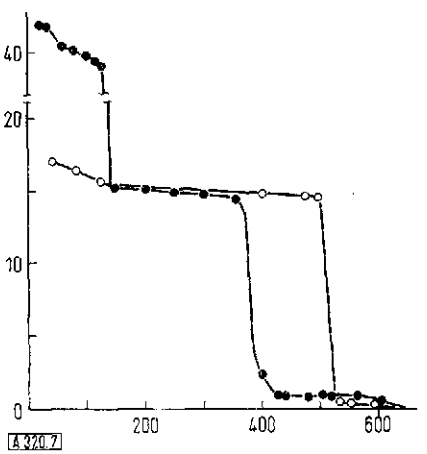


Fig. 6. Thermal decomposition of kaolinite (○—○) and urea-kaolinite (●—●).
Ordinate: Percentage loss in weight referred to sample calcined at 1000 °C.
Abscissa: Temperature [°C].

The properties of the kaolinite intercalation compounds formed during urinary ageing therefore lead to an understanding of the secret of egg-shell porcelain. At the same time, the fact that the favorable ceramic properties increase appreciably only when freshly aged, undiluted, and unwashed kaolin is ground explains how this process could be forgotten or lost so easily and thus acquire the status of a secret.

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Reactions of Olefins with the Titanium-Carbon Bond

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Dedicated to Prof. Dr. Karl Ziegler on the occasion of his 65th birthday

At low temperatures, ethylene and α-olefins (Δ^1-olefins or 1-alkenes) are rapidly converted into oligomers by the two-component organometallic catalyst CH_3TiCl_3-CH_3AlCl_2. To achieve smooth oligomerizations, aromatic or chlorinated hydrocarbons must be used as solvents. Although the activity of the titanium-carbon bond is enhanced by the aluminum component of the catalyst, the aluminum and its methyl group do not participate in the reaction proper; the latter proceeds exclusively at the titanium-carbon bond. The reaction with olefins can be used as an analytical method for the quantitative determination of the titanium-carbon bond in admixture with the organoaluminum component. It is thus possible to follow the reaction leading to formation of the catalyst from titanium tetrachloride, as well as the processes occurring at the titanium-carbon bond during the oligomerization of olefins. All the observations indicate that the catalyst possesses an ionic structure which is determined by the solvent. It is shown that the initial reaction step probably involves formation of a complex between the olefin and the alkyltitanium cation. The reaction scheme proposed is based on organometallic reactions which are characterized by carbanion and hydride transfers within the olefin-cation complex. This mechanism, which is unusual for Ziegler catalysts, is due to the predominance of hydride transfers.

1. Introduction

In a recent report in this journal, we described the low temperature polymerization of ethylene in the presence of the two-component organometallic catalyst CH_3TiCl_3·CH_3AlCl_2 [1]. The significant features which distinguish these catalysts (and their use) from comparable Ti/Al catalyst systems may be summarized as follows:

1. Tetravalency of the titanium component.
2. Homogeneity of the solution system.
3. Use of chlorinated hydrocarbon solvents (CH_2Cl_2, $CHCl_3$).

The activity of this organometallic system is so large that ethylene is rapidly converted into oligomeric olefins even at temperatures as low as −50 to −100 °C. In addition to straight-chain α-olefins, the products consist predominantly of 2-ethyl-1-alkenes. Furthermore, the catalyst makes it possible to achieve highly selective β-ethylation of α-olefins.

Further studies of these reactions have provided results which are of preparative interest and which have given us a better understanding of the reactions that take place between olefins and the titanium-carbon bond. These new results have thus contributed to the explanation of the processes involved in the polymerization of olefins with mixed organometallic catalysts, which was discovered by *K. Ziegler* and his collaborators [2].

[1] *H. Bestian, K. Clauss, H. Jensen*, and *E. Prinz*, Angew. Chem. *74*, 955 (1962); Angew. Chem. internat. Edit. *2*, 32 (1963).

[2] *K. Ziegler* et al., Angew. Chem. *67*, 541 (1955).

2. Oligomerization of α-Olefins

In our previous report on the low temperature polymerization of ethylene [1], we already mentioned that the catalytic solution of CH_3TiCl_3 and CH_3AlCl_2 in methylene chloride assumes a deep-red color upon addition of an α-olefin. The same phenomenon is observed when ethylene is introduced into this catalyst solution. However, whereas the reaction of ethylene at −70 °C is rapid and is accompanied by a vigorous evolution of heat, α-olefins do not react discernibly under comparable conditions. When ethylene is introduced into a catalyst solution containing an α-olefin, the resulting reaction is mainly β-ethylation of the α-olefin. This observation indicates that the CH_3TiCl_3·CH_3AlCl_2 system catalyses the reaction of α-olefins at a rate much slower than that of ethylene. Our latest results show, however, that α-olefins can also be converted into oligomeric olefins at −70 °C. The reaction conditions are similar to those employed with ethylene, but the time allowed for the reaction must be several times longer. The experimental results obtained with several α-olefins are shown in Table 1. It is seen that with the exception of 1-butene, the α-olefins required 15 hours for 50% conversion into oligomers. The mixture of oligomers formed under these conditions contains 60 to 65% of the respective dimer.

In order to obtain better insight into the oligomerization of the α-olefins, we determined the composition and structure of the dimeric and trimeric products from the reaction of 1-butene. The analysis was facilitated by the

Table 1. Oligomerization of α-olefins [*] in CH_2Cl_2 at −70 °C; catalyst: CH_3TiCl_3·CH_3AlCl_2; reaction time: 15 hours; 330 ml of α-olefin, 330 ml of CH_2Cl_2, 15 mmoles of CH_3TiCl_3, and 10 mmoles of CH_3AlCl_2.

Olefin	Conversion to oligomers [%]	Composition of the oligomers (Σ = 100)		
		Dimer [%]	Trimer [%]	Tetramer and higher [%]
1-Butene	27	42	19	39
1-Pentene	45	67	18	25
1-Hexene	49	65	19	16
1-Heptene	51	63	17	20
1-Octene	60	62	38	

[*] The conversion of propylene is abnormal and is therefore not included. The primary oligomerization products of propylene are more reactive than those of the higher α-olefins. Under the reaction conditions employed, they are therefore transformed completely into secondary polymerization products.

fact that the C_8 and C_{12} fractions obtained on working up the mixture of products are comparatively uniform. Analysis of the C_8 fraction (*i.e.* dimeric 1-butene) gave the following composition:

2-ethyl-1-hexene	88%
cis-2-octene	5.5%
trans-2-octene	0.3%
trans-3-octene	appr. 2%
3-methylheptane (= 2-ethylhexane)	appr. 3%

These results indicate that 91% of the dimerization proceeds via head-to-tail coupling (formation of 2-ethyl-1-hexene and 2-ethylhexane). Head-to-head coupling of the 1-butene molecules constitutes about 8% of the dimerization, as shown by the quantity of n-octenes with Δ^2- and Δ^3-double bonds obtained.

Analysis of the dimerization products of 1-pentene and 1-hexene gave similar results (Table 2).

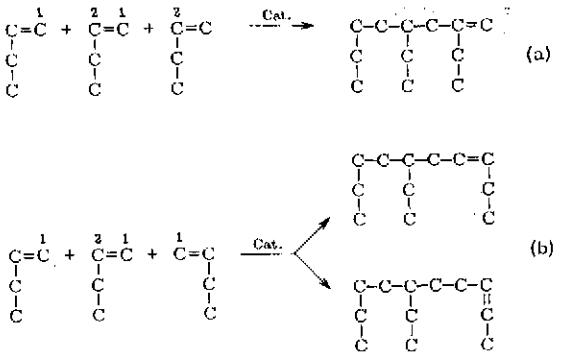
Table 2. Composition of the dimer fractions from oligomerization of 1-pentene and 1-hexene.

Starting olefin	Dimerization products			
	branched		unbranched	
	% present	structure	% present	structure
1-pentene	90	2-(n-propyl)-1-heptene	8	3-decene and 4-decene
1-hexene	90	2-(n-butyl)-1-octene	8	4-dodecene and 5-dodecene

These results exhibit an interesting relationship to the data of *Ziegler* et al. [3], who obtained 4–6% straight-chain by-products on dimerization of α-olefins with triethylaluminum. With a view to elucidating the mechanism of their formation, we were particularly careful in determining the location of the double bond in the straight-chain dimers. In every case, the unbranched fraction of the dimer consisted of two isomeric olefins differing in the position of the double bond. It is evident that the position of the double bond is related to the nature of the starting olefin. Head-to-head coupling of the two α-olefin molecules evidently fixes the double bonds at two definite locations at which they remain even under the influence of the catalyst.

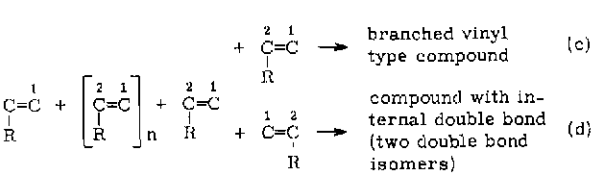
[3] *K. Ziegler* et al., Liebigs Ann. Chem. 629, 143 (1960).

A combination of analytical methods enabled us to elucidate to a large extent the composition of the C_{12} fraction of the oligomerization product obtained from α-butylene (1-butene). Thus, hydrogenation yielded a 70:30 mixture of two hydrocarbons, which were identified as 2,4-diethyloctane (3-methyl-5-ethylnonane) and 5-ethyldecane by comparison with synthetically prepared hydrocarbons. Infrared spectra indicated that the double bond is present predominantly as branched vinyl groups ($H_2C{=}\underset{|}{C}-$). The analytical results showed that the C_{12} fraction, like the C_8 fraction, comprises only a few components. Disregarding geometric isomerism, it appears that only three olefins with two different carbon skeletons are present. On the basis of these results, the following reaction scheme may be assumed to describe the trimerization:



The predominant reaction is that involving normal coupling of α-olefin molecules, *i.e.* via the 1–2–1–2 scheme [Reaction (a)], about 70% of the product being formed by this route. The remaining 30% are due to the unusual 1–2–1–1 linking of Reaction (b). Thus, the trimers formed according to (b) are produced in a two-step reaction, *viz.* a normal head-to-tail coupling (identical to dimerization) followed by a head-to-head linking. It may be assumed with a great degree of certainty that head-to-head coupling always results in chain termination, with formation of an internal double bond. Normal coupling [Reaction (a)] results in chain growth and, when terminated, produces oligomeric olefins with a branched vinyl group.

It seems reasonable to assume that the higher oligomers are also formed via the general scheme of Reactions (a) and (b). The growth reaction always follows the 1–2 route. Structural differentiation occurs only during the addition of the last molecule of α-olefin onto the chain.



Again, infrared studies have shown that the branched vinyl-type structure also predominates in the higher fractions. We have not yet been able to obtain a detailed structural analysis of the tetramer and pentamer series.

3. Isomerization of α-Olefins

In our previous communication [1], we discussed the question whether the $CH_3TiCl_3 \cdot CH_3AlCl_2$ catalyst is capable of shifting olefinic double bonds under the conditions of the low-temperature polymerization. The results obtained in the ethylation of α-olefins have proved unequivocally that isomerization of a Δ^1-double bond does not occur under the conditions used, *i.e.* in the presence of ethylene.

It was therefore very surprising to find that the unreacted fraction from the oligomerization of α-olefins contained considerable amounts of olefins with a Δ^2-double bond. Thus, the oligomerization is obviously accompanied by a side reaction resulting in a shift of the double bond in the starting α-olefin (Table 3).

Table 3. Isomerization of α-olefins in CH_2Cl_2 at −70 °C. (Catalyst and reaction conditions as described in Table 1).

Starting olefin	Conversion [*] to		Composition of the isomeric product (Σ = 100 %)	
	Oligomers [%]	Isomers [%]	*cis*-2-olefin	*trans*-2-olefin
1-butene	27	8	96	4
1-pentene	45	16	88	12
1-hexene	49	14	90	10
1-heptene	51	17	87	13
1-octene	60	16	86	14

[*] Based on the α-olefin charged.

It is evident from Table 3 that the oligomerization and the shifting of the double bond occur as coupled reactions. The observed data can be explained unequivocally by a reaction mechanism which will be described below. The rates of the two reactions (Table 4) and the dependence of the reaction on the solvent (Table 5) were investigated.

Table 4. Rates of oligomerization and isomerization of 1-pentene in CH_2Cl_2 at −70 °C (110 ml of 1-pentene, 110 ml of CH_2Cl_2, catalyst mixture consisting of 10 mmoles each of $TiCl_4$ and $(CH_3)_2AlCl$, prepared at 20 °C).

	Reaction time					
	5 min	15 min	1 h	2 h	6 h	16 h
Amount isomerized [% 1-pentene]	0.5	1	3	5	10	18.5
Amount oligomerized [% 1-pentene]	3	3–4	10	20	50	70
Amount unconverted [% 1-pentene]	96	94	85	75	40	11

Table 5. Dependence of the isomerization and oligomerization of 1-pentene on the solvent [*] (Catalyst and reaction conditions as described in Table 4).

	Solvent		
	Methylene chloride	Chloroform	Toluene
Reaction time [h]	20	20	20
Isomerization [%]	18	14	4
Oligomerization [%]	70	45	10
Unconverted 1-pentene [%]	8	38	85

[*] No reaction could be observed in heptane.

Our results can be summarized briefly as follows:

1. Approximately 50% conversion of the α-olefin to oligomeric products is accompanied by simultaneous formation of about 15% of isomeric olefins.

2. The double bond is shifted selectively from the Δ^1- to the Δ^2-position. A further shift of the bond to the center of the molecule is apparently not possible.

3. The Δ^2-double bond formed is almost entirely (about 90%) of the energy-rich *cis*-variety. Formation of the *trans*-configuration is strongly depressed.

4. The rate of reaction is strongly dependent upon the solvent. The rate decreases in the order methylene chloride > toluene > heptane.

Since the rate of the reaction between ethylene and α-olefins exceeds those of the oligomerization and isomerization by several orders of magnitude, the observed fact that α-olefins do not undergo the latter two reactions to any significant extent in the presence of ethylene becomes readily understandable.

4. Reactivity of the Titanium-Carbon Bond

In our communication on the low-temperature polymerization of ethylene [1], we showed that the effective catalyst, the two-component organometallic system $CH_3TiCl_3 \cdot CH_3AlCl_2$, remains unchanged during polymerization at −50 to −100 °C. This observation is valid for the valence of the titanium, but we took it to hold also for the methyl groups present on the catalyst. Our experimental results seemed to support the view that the methyl groups do not participate in the polymerization. This assumption was also based on the reaction conditions and the composition of the polymeric olefins, neither of which seemed related to the Ziegler-type anionic polymerization.

Since the problem whether the methyl groups of the mixed catalyst remain unchanged in the olefin reactions is of primary importance in determining the mechanism of its action, our later work used considerably more refined procedures. The new results indicate unequivocally that only one-half of the original methyl groups still remain in the mixed $CH_3TiCl_3 \cdot CH_3AlCl_2$ catalyst after the reaction with ethylene or an α-olefin in methylene chloride at −70 °C. This was our first experimental indication that the olefin reaction takes place at a metal-carbon bond in this system as well.

a) Reaction Site

The special position which the system $CH_3TiCl_3 \cdot CH_3AlCl_2$ occupies among mixed organometallic catalysts made it possible to determine the active center of these two-component systems, a problem that is of fundamental importance. Experimental proof becomes possible in this case because the reactions with ethylene or an α-olefin can be carried out in a temperature range in which ligand interchange between the metal atoms

does not occur. In principle, the method consists of treating the catalyst mixture with ethylene or an α-olefin in methylene chloride at −70 °C. The alkyl group at the active metal site is thereby removed by reaction with the olefin. The alkyl group at the inactive site is not disturbed and may be determined as the corresponding saturated hydrocarbon after treatment of the mixture with alcohol.

To determine whether it is the Ti–C or the Al–C bond that reacts in the $CH_3TiCl_3 \cdot CH_3AlCl_2$ mixture, varying molar ratios of the two compounds were dissolved in methylene chloride at −80 °C. The resultant mixtures were then studied by the method described above. The molar ratio Ti:Al was varied between 0.2 and 5. At all Ti:Al ratios, the quantity of methane liberated after treatment with alcohol was exactly equivalent to the quantity of CH_3AlCl_2 present. It was thus shown that the methyl groups attached to the aluminum remain unchanged during the olefin reaction. The reaction therefore proceeds exclusively at the titanium-carbon bond.

The determination of the active site is even simpler when CH_3AlCl_2 is replaced by $C_2H_5AlCl_2$ in the catalyst mixture, *i.e.* when the metal atoms are labelled with different alkyl groups. Treatment of an equimolar solution of the two catalyst components in methylene chloride with 1-pentene at −70 °C and subsequent decomposition with methanol yields ethane in a quantity corresponding exactly to the initial amount of $C_2H_5AlCl_2$; only traces of methane are evolved.

b) The Fate of the Methyl Group

When it became clear that the active site of the catalyst system is the titanium-carbon bond, it also became possible to determine the fate of the methyl group attached to the titanium atom. This was done by allowing stoichiometric quantities of 1-pentene and mixed catalyst to react in methylene chloride at −70 °C and then decomposing the reaction mixture with an alcohol. The products were identified as 2-methylpentane and n-pentane. The formation of these two compounds can be regarded as proof of the mechanism shown in Equation (e).

$$Ti{-}CH_3 \xrightarrow{+\,C_5H_{10}} Ti{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CH_2{-}CH_2{-}CH_3 \xrightarrow{+\,C_5H_{10}}$$

$$Ti{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_3 + CH_2{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}CH_2{-}CH_2{-}CH_3 \qquad (e)$$

No 2-methylpentane is found among the reaction products when an excess of 1-pentene (*e.g.* $Ti:C_5H_{10} = 0.2$) is used. The quantity of pentane produced passes through a maximum. 2-Methyl-1-pentene cannot be detected in the products either. 2-Methyl-1-alkenes are much less stable in the catalyst solution than other olefins containing an ethyl or an even larger alkyl group in the 2-position and are rapidly converted into higher oligomers.

In this way, the methyl groups present on the titanium component disappear in the higher polymerization products and cannot be identified. This is the explanation for our previous results, where the methyl groups of the catalyst could not be detected in the low oligomers produced with a large excess of the appropriate olefin.

c) The Reaction of Olefins with the Ti–C Bond as an Analytical Method

The observation that olefins react only with the Ti–C bond at low temperatures can be used as an analytical method for the determination of the organometallic titanium component in the catalyst mixture (see Experimental Section). Among other things, this has permitted a closer study of the equilibrium reactions of the components of the catalyst. Reaction (f) may be regarded as that forming the catalyst from the compounds on the left-hand side of the equation:

$$TiCl_4 + (CH_3)_2AlCl \rightleftarrows CH_3TiCl_3 + CH_3AlCl_2 \qquad (f)$$

$$TiCl_4 + CH_3AlCl_2 \rightleftarrows CH_3TiCl_3 + AlCl_3 \qquad (g)$$

The first point studied was the rate of ligand interchange between the two metal atoms, *i.e.* the time required for the establishment of equilibrium between the components of the catalyst system. We used mainly Reaction (f) to examine this question since the active catalyst system is formed in this reaction starting from $TiCl_4$ and $(CH_3)_2AlCl$. Previous results [1] had already established that the ligand interchange of Reaction (f) is retarded or even stopped at low temperature. We now obtained quantitative proof of this observation. Thus, when $TiCl_4$ and $(CH_3)_2AlCl$ (each in a concentration of 0.1 mole/l) are allowed to interact for 2 hours in methylene chloride at −70 °C, about 5 % CH_3TiCl_3 (based on $TiCl_4$) is formed. The ligand interchange is therefore not completely suppressed even at −70 °C, a fact which must be compensated for in the analytical determination of the Ti–C bond by selection of suitable reaction conditions (lower concentration, shorter reaction with the olefin). The rate of ligand interchange increases rapidly with temperature. At −45 °C, the equilibrium is established to the extent of 43 %, and at −30 °C, it reaches approximately 90 %. At room temperature, particularly when higher concentrations of the starting materials are used, the rate of ligand exchange is very rapid. At 20 °C and a 1 M concentration of $TiCl_4$ and $(CH_3)_2AlCl$, complete equilibrium is attained after 1–2 minutes.

To determine the equilibrium distribution in Reactions (f) and (g) at the desired temperature, we allowed sufficient time for the system to attain equilibrium, preferably at high concentrations of the components. The mixture was then rapidly quenched by cooling to −70 °C and the concentration of Ti–C bonds was found by treatment with an olefin. Figure 1 shows the equilibrium concentration of CH_3TiCl_3 in Reaction (f) as a function of the molar ratio of the starting materials $TiCl_4$ and $(CH_3)_2AlCl$.

The same results as those shown in Figure 1 are obtained when the equilibrium is established starting from CH_3TiCl_3 and CH_3AlCl_2. The relationship represented

in Figure 1 can be used to calculate the equilibrium constant of Reaction (f).

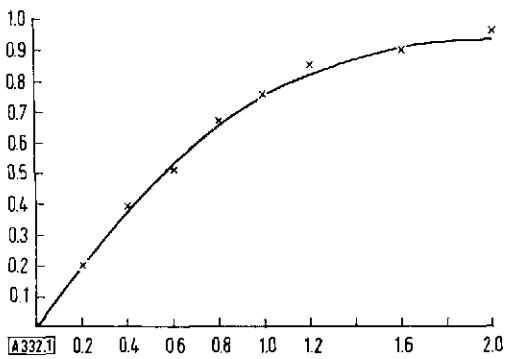


Fig. 1. $TiCl_4 + (CH_3)_2AlCl \rightleftarrows CH_3TiCl_3 + CH_3AlCl_2$
Equilibrium concentration of CH_3TiCl_3 as a function of the molar ratio of Al:Ti at 20 °C in CH_2Cl_2. [Ti] = 1 mole/l.
Ordinate: Concentration of CH_3TiCl_3 [mole/l].
Abscissa: Molar ratio of Al:Ti.

The result obtained at the extreme Al:Ti mole ratio of 0.2 should be disregarded for purposes of calculation since it could not be determined with sufficient accuracy. When the values taken from the ordinate of the curve are used to calculate the equilibrium constant and results are averaged, the equilibrium constant for Reaction (f) is found to be almost exactly 10. This value holds for the reaction in methylene chloride at 20 °C. *Groenewege* [4] attempted to determine the equilibrium of Reaction (f) from infrared measurements. His studies were made in heptane and carbon tetrachloride using KBr cell windows because of the presence of CH_3AlCl_2. His value of 1 for the equilibrium constant is certainly too low. *Groenewege* himself admits that this value is no more than a rough estimate.

A solution of $TiCl_4$ (1 mole/l) and CH_3AlCl_2 (1 mole/l) in methylene chloride was used to determine the equilibrium constant of Reaction (g). The equilibrium concentration of CH_3TiCl_3 at 20 °C was found to be 0.085 mole/liter. On introducing the appropriate values into

$$K = \frac{[CH_3TiCl_3]\cdot[AlCl_3]}{[TiCl_4]\cdot[CH_3AlCl_2]}$$

we found the equilibrium constant to be 0.86×10^{-2} (in CH_2Cl_2 at 20 °C). The quantity of CH_3TiCl_3 (8.5 mole-% of the titanium) formed in Reaction (g) is so large, that it must be taken into consideration when calculating the status of the equilibrium of Reaction (f) at small molar ratios (Al:Ti<0.6). The correction factor [5] for the equilibrium constant of Reaction (f) amounts to 0.89 for Al:Ti = 0.6 and to 0.74 for Al:Ti = 0.4. The constant for Reaction (g), which is affected by Reaction (f), must be corrected accordingly, the factor at Al:Ti = 1 being 1.12.

Surprising results were obtained when the equilibrium distributions and the rates of Reaction (f) were studied in other solvents. We found that the equilibrium is dependent upon the solvent (Table 6). The farthest shift towards the active catalyst components occurs in methylene chloride and toluene. In heptane, the equilibrium concentration of CH_3TiCl_3 is appreciably lower.

In a 0.1 M solution of the catalyst mixture in heptane, the half-life of the reaction at 20 °C is about 2 minutes; in methylene chloride at half this concentration, it is

Table 6. $TiCl_4 + (CH_3)_2AlCl \rightleftarrows CH_3TiCl_3 + CH_3AlCl_2$
Dependence of the equilibrium on the solvent (20 °C; molar ratio Al:Ti = 1; [Ti] = 1 mole/l).

Solvent	Equilibrium concentration of CH_3TiCl_3 [mole/l]	Equilibrium constant K
Methylene chloride	0.76	10
Toluene	0.74	8
n-Heptane [*]	0.66	3.7

[*] After quenching to −70 °C, the concentration of Ti—C bonds was determined in methylene chloride or toluene, since no reaction of olefin with the Ti—C bond can be obtained in heptane.

The rate at which equilibrium is established is also strongly dependent on the solvent (Fig. 2).

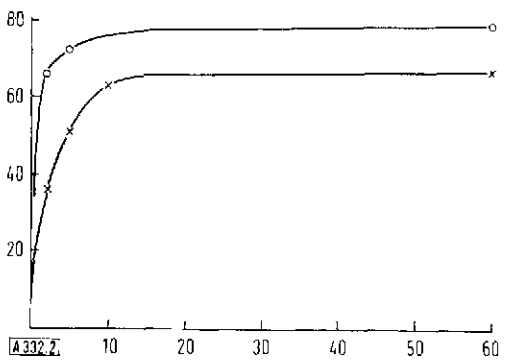


Fig. 2. $TiCl_4 + (CH_3)_2AlCl \rightleftarrows CH_3TiCl_3 + CH_3AlCl_2$.
Rate of formation of CH_3TiCl_3 in heptane (x) and methylene chloride (o) at 20 °C. (Molar ratio Ti:Al = 1; [Ti] = 0.1 mole/l in heptane, 0.05 mole/l in CH_2Cl_2).
Ordinate: Mole-% CH_3TiCl_3 (Total Ti = 100).
Abscissa: Reaction time [min].

less than one minute, as ligand exchange takes place much faster in a polar than in a non-polar medium. This observation seems to indicate that the ligand exchange is an ionic process.

5. The Titanium-Carbon Bond and its Activation

After the high activity of the titanium-carbon bond in the two-component system had been established, we wanted to find out whether the titanium component alone, *i.e.* without activation by the other component, could react with olefins. In collaboration with *C. Beermann* [6,7], we discovered that under the conditions of Ziegler polymerization, methyltitanium trichloride initiates the polymerization of ethylene in aliphatic hydrocarbons only when a sufficient quantity of titanium trichloride has been formed by partial decomposition [6]. The resulting polyethylene is of high molecular weight and is largely unbranched. The aluminium-free two-component system $TiCl_3\cdot CH_3TiCl_3$ may be conceived as the catalyst in this polymerization.

We repeated the attempts to react ethylene with methyltitanium trichloride, this time, however, at low temperature. This was done to prevent the formation of titanium trichloride, *i.e.* the appearance of a new cata-

[4] *M. P. Groenewege*, Z. physik. Chem. N.F. *18*, 158 (1958), footnote 17.

[5] *D. Langbein*, unpublished work.

[6] *C. Beermann* and *H. Bestian*, Angew. Chem. *71*, 618 (1959).

[7] German Patent 1023766 (Dec. 16th, 1955), Farbwerke Hoechst AG.

lyst system. As with the Ti^{IV}/Al system, we found that the solvent had a decisive effect on the initiation and course of the olefin reaction. The experiments were performed at normal pressure by introducing ethylene into a 0.25 M solution of CH_3TiCl_3 at −70 °C. In heptane, no reaction was observed after four hours; in toluene, ethylene was introduced at a ratio of 6 moles/mole of CH_3TiCl_3, and 97 % of the olefin was converted within the four-hour period; in methylene chloride, 90 % conversion of the ethylene had occurred after only 45 minutes. The process involved here – particularly when toluene is the solvent – is essentially a chain growth reaction resulting in an unbranched molecule which is mainly attached to titanium. Because of their low solubility in toluene compared to methyltitanium trichloride, the nascent alkyltitanium halides precipitate and may be separated as a mixture.

The following results were obtained on analysis of such an alkyltitanium trichloride mixture, prepared in toluene at −70 °C, with 6 moles of ethylene:

1. The alkyl group is unbranched and on the average contains 15 carbon atoms.

2. Alkyl groups with an odd number of carbon atoms predominate; the distribution curve shows a pronounced maximum at a chain length of C_{15} and C_{17}.

3. About 20 % of the alkyl groups have an even number of carbon atoms. The distribution curve for this group is flatter and has a maximum at C_{16}.

The observation that an appreciable amount of alkyl chains with an even number of carbons is formed indicates that, in addition to chain growth, chain transfer reactions also occur here [see Reactions (h), (i), and (k)]:

$$CH_3TiCl_3 \xrightarrow{+C_2H_4} CH_3-(CH_2-CH_2)_n-TiCl_3 \quad (h)$$
$$(1)$$

$$(1) \xrightarrow{+C_2H_4} \underset{(2)}{CH_3-CH_2-TiCl_3} + CH_3-(CH_2-CH_2)_{n-1}-CH=CH_2 \quad (i)$$

$$(2) \xrightarrow{+C_2H_4} CH_3-CH_2-(CH_2-CH_2)_n-TiCl_3 \quad (k)$$

Analysis of the reaction mixture after decomposition with alcohol gives a distribution curve for the α-olefins with an odd number of carbons with a maximum at C_7.

In addition to the higher rate of reaction, a change in the mode of chain growth is observed in methylene chloride. Branched alkyl residues and α-olefins are formed besides the straight-chain products, apparently by insertion of the α-olefins formed by Reaction (i).

The extent to which the Al component activates the Ti–C bond in the reaction with olefins was determined nearly quantitatively in the following experiment: we measured the half-life (*i.e.* the time necessary for the disappearance of one-half of the methyl groups attached to the titanium atom) for the reaction of α-pentene with the Ti–CH_3 bond in methylene chloride at −70 °C. For a 0.1 M solution of CH_3TiCl_3, the half-life was 300 minutes; the corresponding value for the catalyst system $CH_3TiCl_3 \cdot CH_3AlCl_2$ was about 1 minute. Thus, under the above conditions, the Al component increases the activity of the Ti–C bond in methyltitanium trichloride by a factor of 300.

6. Reaction Mechanism

a) The Active Structure within the Catalyst

The following observations, made mostly at low temperature, should be borne in mind in any consideration of the active structure of the Ti^{IV}/Al system:

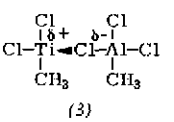
1. The active site of the reaction is the titanium atom. The olefin reacts with the Ti–C bond.

2. The Al component increases the activity of the Ti component without participating in the reaction.

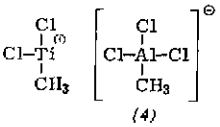
3. The solvent has a strong effect on the rate of the reaction. The activity of the catalyst decreases in the order chlorinated hydrocarbons > aromatic hydrocarbons > paraffinic hydrocarbons.

4. Addition of the olefin causes a darkening of the active catalyst solution.

These facts are best explained by assuming an ionic structure for the catalyst, such as *(3)* or *(4)*.



(3)



(4)

In these structures, the aluminum component claims the electrons of one chlorine atom of the methyltitanium trichloride, thus increasing the positive charge of the titanium atom [Structure *(3)*].

The tremendous increase in the activity of the system caused by toluene and especially by chlorinated hydrocarbons such as methylene chloride or chloroform (without which the reaction with olefins would not proceed at all at low temperature) can be explained in a simple fashion by assuming solvation of the titanium cation by these solvents. This view is supported by the observation that cooling of a solution of the catalyst mixture in toluene or methylene chloride to −70 °C causes a marked deepening of the color. This color intensification disappears upon rewarming – the process is completely reversible and can be repeated as often as desired; this effect may indicate the presence of solvated Ti^{IV} cations. The completely ionized structure *(4)* should thus also be considered as a genuine active species. This limiting form of the catalyst system is probably the most active one.

Uelzmann [8] has pointed out that an increase in electron affinity should be expected in the series $(TiCl)^+$, $(TiCl_2)^+$, and $(TiCl_3)^+$, since the number of electrons necessary for the formation of an octet decreases with rising valence of the titanium atom. When this deliberation is applied to the

[8] *H. Uelzmann*, J. Polymer Sci. *32*, 457 (1958).

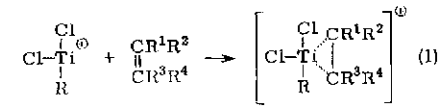
$(CH_3TiCl_2)^+$ cation, the observed color phenomena are readily explained by assuming the formation of cationic complexes with the solvent.

b) Activation of the Olefin

The color intensification observed on addition of olefins to the catalyst solution is highly significant for the initiation and subsequent course of the reaction. The following observation is especially noteworthy.

The color change caused by addition of an α-olefin (yellow → dark red) is observed only in solvents in which the olefin reaction actually does take place. The color intensifies very rapidly in methylene chloride, somewhat slower in toluene, and is hardly noticeable in heptane. The color change seems to precede the olefin reaction.

We interpret these and other observations on the color reaction by assuming that the olefin molecule becomes attached to the cationic titanium atom of the catalyst by its π-electrons prior to its reaction with the titanium-carbon bond. So far, it is impossible to decide whether the olefin is attached to a free titanium cation or merely to a strongly positive titanium atom, but this problem is not of really fundamental importance. However, because of the solvent effects observed, we are inclined to write the reaction with a free cation (I).



(I)

So far, all the observations made point to the conclusion that the coupling of the olefin with the titanium cation – discernible by the intensification of the color – is a prerequisite for the reaction with the Ti–C bond. This process [Reaction (I)] may be considered as the activation step of the reaction. The assumption of this step facilitates our understanding of the rapid and unusual course of the olefin reaction with organometallic systems of tetravalent titanium activated by Al.

Several of the mechanisms proposed for the Ziegler-type polymerization have already used the concept of a coupling of the π-electron system of an olefin with the titanium atom of the Ti/Al mixed catalyst and have thus explained the initiation of the organometallic polyreaction. *Patat* and *Sinn* [9] prefer to think of the catalyst as a non-ionic, complexed structure, characterized by a carbon bridge. This concept is not satisfactory for explaining the processes occuring in the Ti^{IV}/Al system. On the other hand, the ionic hypothesis of *Uelzmann* [8] does not take into consideration the fact that an alkyl group on the titanium is necessary both for the activation and for the reaction. The hypothesis closest to our own ideas is that of *Breslow* and *Newburg* [10]; using biscyclopentadienyltitanium dichloride as an example of the Ti component of the Ti/Al system, they arrive at a mechanism involving preliminary formation of a π-complex between the olefin and positively charged titanium, followed by chain growth at the Ti–C bond. However, even in this case there is no real analogy with the simple Ti^{IV}/Al catalyst. The two-component system $(C_5H_5)_2Ti(CH_3)Cl{\cdot}CH_3AlCl_2$ already undergoes the color change from yellow to red during its formation from its components. In contrast to our catalyst, the *Breslow-Newburg* catalyst changes color even in saturated hydrocarbons and the system does not become darker on addition of an olefin. Thus, the complex cation is present in the cyclopentadienyltitanium catalyst right from the very start and should presumably exhibit little inclination to accept additional π-electrons from olefins. This should explain why the cyclopentadienyltitanium(IV) catalysts do not initiate the oligomerization of olefins in methylene chloride at low temperatures.

c) The Mechanism of the Polyreaction

In view of the unusual conditions and the unusual course of the reaction, which bears no relationship to the processes occurring with Ziegler catalysts, we previously postulated an ethylene oligomerization mechanism which excluded participation of the Ti–C bond [1]. The previous hypothesis that olefins which are activated by π-complex formation with the titanium cation form short-lived intermediates which become stabilized as oligomeric olefins by hydride or proton shifts has been invalidated by the new findings on the reactivity of the titanium-carbon bond described above. These new results leave no doubt that the system CH_3TiCl_3-CH_3AlCl_2 should be included in the family of the Ziegler catalysts. This allocation was initially somewhat difficult because the chain growth reaction is accompanied even at low temperatures by a rapid chain transfer process which yields α-olefins that are capable of reacting with additional molecules of ethylene to give either branched α-olefins or olefins with internal double bonds.

By using approximately stoichiometric ratios of the reactants, we have been able to obtain experimental clarification of the initial steps of the reaction between ethylene and the $Ti-CH_3$ bond (Table 7).

The results shown in Table 7 enabled us to deduce the processes involved in the intial reaction (CH_3Ti → C_2H_5–Ti) and gave a first insight into the actual polyreaction of ethylene. We shall dispense with a discussion of the mechanism of the initiation reaction, since it is identical with the processes involved in the polymerization scheme starting with the C_2H_5-Ti group. The data of Table 7 should, however, be clarified by the following additional observations:

1. The first step (m) in the organometallic reaction is only slightly inhibited.

$$CH_3\text{–}Ti \xrightarrow{+\,C_2H_4} CH_3\text{–}CH_2\text{–}CH_2\text{–}Ti \qquad (m)$$

This observation is significant in view of the results obtained in the reaction of trimethylaluminum with ethylene [11].

2. Olefins formed by replacement of the alkyl groups attached to the titanium cannot be detected among the reaction products. Propylene was conspicuously absent. From comparative experiments it may be concluded that α-olefins react very rapidly with the Ti–C bond under the conditions of Table 7 (CH_3–Ti, C_2H_5–Ti,

[9] *F. Patat* and *H. Sinn*, Angew. Chem. *70*, 496 (1958).

[10] *D. S. Breslow* and *N. R. Newburg*, J. Amer. chem. Soc. *81*, 81 (1959).

[11] *K. Ziegler* et al., Liebigs Ann. Chem. *629*, 132 (1960).

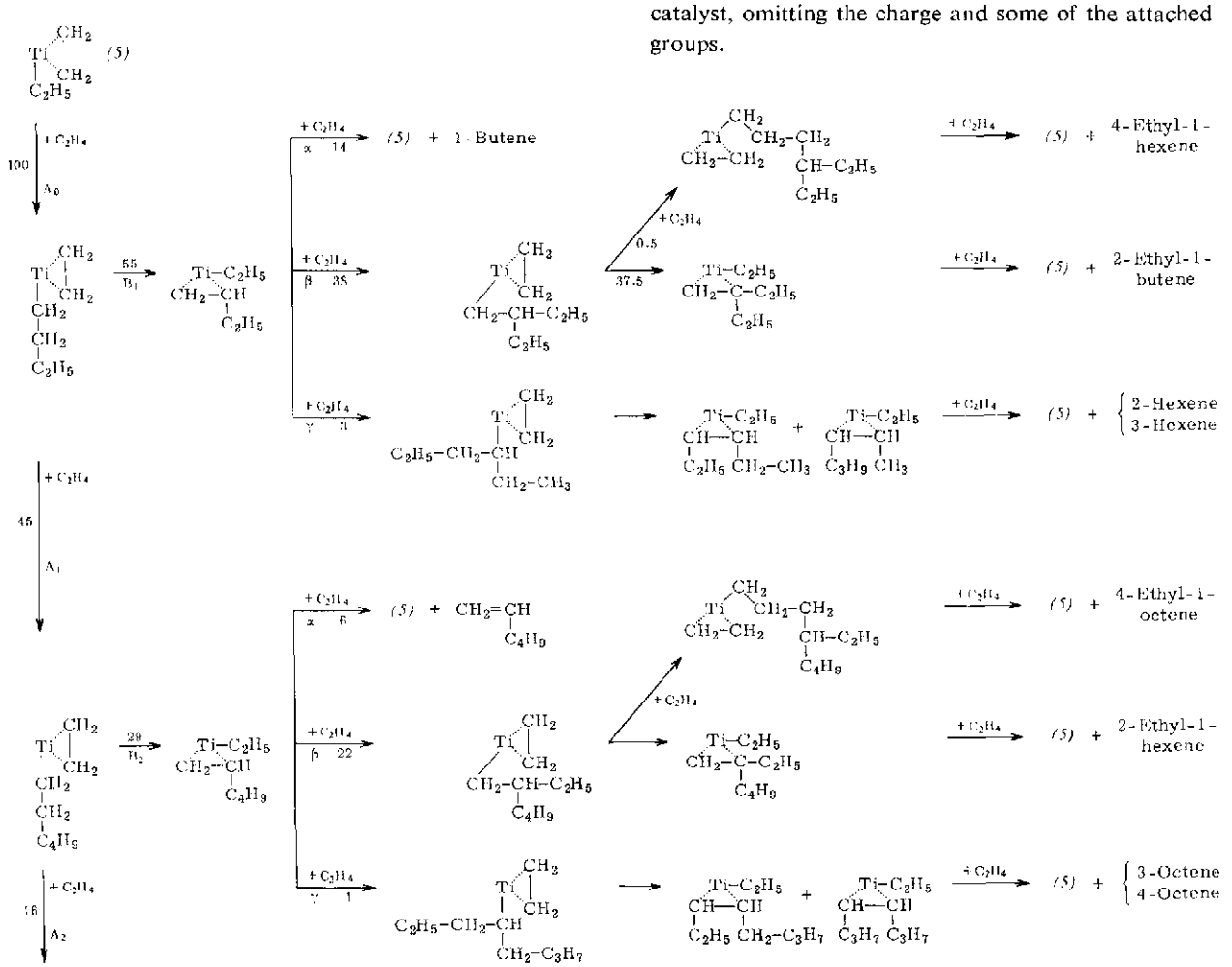
Table 7. Products of the reaction between ethylene and the $CH_3TiCl_3 \cdot CH_3AlCl_2$ catalyst at −70 °C as a function of the quantity of ethylene used [*]. (CH_3TiCl_3 concentration kept constant at 38 mmoles/100 ml of CH_2Cl_2; Ti:Al = 1).

Reaction products after methanolysis	Quantity [mmoles] obtained when using			Ti—R prior to methanolysis (derived from column 1)
	25 mmoles of C_2H_4 (C_2H_4:Ti=0.66)	50 mmoles of C_2H_4 (C_2H_4:Ti = 1.32)	100 mmoles of C_2H_4 (C_2H_4:Ti = 2.64)	
Methane, total	63	56	46	
from Ti-CH_3	25	18	8	Ti—CH_3
Ethane	7.5	11	13	Ti—CH_2—CH_3
Propylene	—	—	—	
Propane	4.5	2.5	1.5	Ti—$(CH_2)_2$—CH_3
n-Butane	1.25	5	9	Ti—$(CH_2)_3$—CH_3
i-Butane	0.02	—	—	Ti—CH_2—$CH(CH_3)_2$
n-Pentane	0.6	0.75	0.7	Ti—$(CH_2)_4$—CH_3
i-Pentane	0.4	0.4	0.2	Ti—CH_2—$CH(CH_3)$—CH_2—CH_3
n-Hexane	—	0.3	1	Ti—$(CH_2)_5$—CH_3
3-Methylpentane	—	0.5	2.5	Ti—CH_2—$CH(C_2H_5)_2$
3-Methylhexane	—	0.25	0.3	Ti—CH_2—$CH(C_2H_5)$—$(CH_2)_2$—CH_3
Hydrocarbons > C_7 and polymer	ca. 0.3 g	ca. 0.8 g	1.8 g	

[*] 100 % conversion is reached after a reaction time of as little as 10 minutes.

etc.) to form 2-alkyl-1-alkenes, which are converted by the catalyst into higher oligomers or into polymeric products.

The processes occurring during the oligomerization of ethylene are shown in Scheme 1. To simplify the diagram, we have shown only the active center of the catalyst, omitting the charge and some of the attached groups.



Scheme 1. The oligomerization of ethylene. The figures below the arrows show the moles of ethylene reacting in the given direction per 100 moles of ethylene entering the total reaction.

When the reaction of ethylene with the catalyst is not interrupted approximately at the stoichiometric stage, *i.e.* when the reaction is transformed into a catalytic process by the introduction of large quantities of the olefin, then the olefins listed in Table 8 are obtained as the products [1].

This scheme is consistent with all the experimental data. Furthermore, the individual processes postulated in it conform to those discovered by *Ziegler* et al. [12] in their study of the reactions of olefins with the aluminum-carbon bond.

[12] *K. Ziegler* et al., Liebigs Ann. Chem. *629*, 121 et seq. (1960).

Table 8. Products of the polymerization of ethylene in CH_2Cl_2 at −70 °C. Catalyst: $CH_3TiCl_3 \cdot CH_3AlCl_2$ (0.045 M Ti, 0.045 M Al); 400 ml of CH_2Cl_2; 100 g of C_2H_4/h; duration of the experiment: 6 h; ethylene conversion: 84 %.

Fraction	Yield based on ethylene conversion	Composition of fraction
C_4	14 %	100 % 1-butene; no 2-butene
C_6	39 %	15 % 1-hexene 6 % 2-hexene 1 % 3-hexene 78 % 2-ethyl-1-butene
C_8	21 %	7.5 % 1-octene 1 % 2-octene 6.5 % 3-octene + 4-octene 82 % 2-ethyl-1-hexene 3 % 4-ethyl-1-hexene
C_{10}	7 %	10–12 % 1-decene (+ 4-ethyl-1-octene) 1 % 2-decene 5 %–8 % 3-decene + 4-decene appr. 1 % 5-decene appr. 80 % 2-ethyl-1-octene (+ 2,4-diethyl-1-hexene)
$>C_{10}$	19 %	chiefly oligomers formed from the 2-ethyl-1-alkenes of the C_8-, C_8-, and C_{10}-fractions (about $^2/_3$ of the total)

The high rate of the processes occurring at the titanium is surprising. The titanium-carbon bond of the system $RTiCl_3 \cdot CH_3AlCl_2 \cdot CH_2Cl_2$ converts 3 moles of ethylene/minute at −70 °C. The growth reaction of the aluminum trialkyls, on the other hand, is relatively very slow, only 1 mole of ethylene being absorbed per hour even at 100 °C and 80–90 atm.

The scheme has the following main characteristics:

1. Chain growth in the sense of reactions A_0, A_1, A_2 ... is accomplished by transfer of the carbanion to the complexed ethylene.

2. Chain transfer reactions B_1, B_2 ... are the result of hydride transfer from the β-carbon atom of the alkyl group to the olefin.

3. The ethyltitanium-α-olefin complexes formed according to B are transformed by three processes:

α) Displacement of the α-olefin from the π-complex by ethylene.

β) Addition of the ethyl anion onto the β-carbon atom of the olefin according to Markownikoff's rule (β-ethylation).

γ) Addition of the ethyl anion onto the α-carbon atom of the olefin ("anti-Markownikoff" addition).

The ethylene complex of the ethyltitanium cation is regenerated in all of these processes.

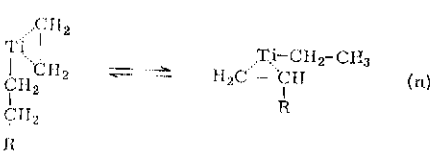
The alkyl groups formed according to 3 γ) are particularly readily displaced by ethylene and yield the straight-chain olefins with internal double bond. The 2-ethylalkyl group formed according to 3 β) exhibits a remarkable behavior. Its removal in the form of a 2-ethyl-1-alkene via hydride transfer and subsequent displacement is accompanied to a slight extent by a growth step in the sense of the A-reactions. This results in the formation of a 4-ethylalkyl group on the titanium, which reacts further in the same way as the unbranched alkyl groups. 4-Ethyl-1-alkenes were identified in the C_8- and C_{10}-fractions as products of this side-reaction.

The results of Table 8 permit calculation of the relative contribution of the various individual processes of the Scheme to the total reaction. A correction must be introduced for the 2-ethyl-1-alkenes, since these olefins undergo secondary polymerization and consequently their quantity in the product does not reflect the amount originally present prior to the polymerization. The correction can be estimated from the composition of the $>C_{10}$-fraction. After the correction is made, the contributions of the various reactions can be calculated as shown by the numbers on the arrows in Scheme 1.

These numbers give the moles of ethylene reacting in a given direction per 100 moles of ethylene entering the total reaction.

This quantitative examination of the processes involved shows that the chain transfer reactions (B_1, B_2 ...) proceed at a higher rate than the chain propagation (A_1, A_2 ...). The number of chains growing without branching is more than halved with each consecutive step. The ease of transfer of hydride ion from the β-carbon atom of the alkyl chain to the olefin is extremely high compared to that encountered in the Ti^{III}/Al systems. The quantitative relationship between the reactions also serves to clarify the second significant characteristic of the scheme. After hydride transfer (Reactions B_1, B_2 ...) the α-olefin remains attached to the titanium with a relatively strong bond. The rate of its displacement by ethylene is slow compared to that of transfer of the ethyl anion to the α- and β-carbon atoms of the complexed α-olefin (ratio of displacement: transfer = 1:3). Straight-chain growth thus degenerates and the resulting irreversible reactions lead to the formation of branched α-olefins and olefins with internal double bonds. These are almost unaffected by the catalyst in the presence of ethylene.

In conclusion, it is worth mentioning that the hydride transfer in steps B_1, B_2 ... is slightly reversible and thus may be expressed by an equilibrium reaction (n).

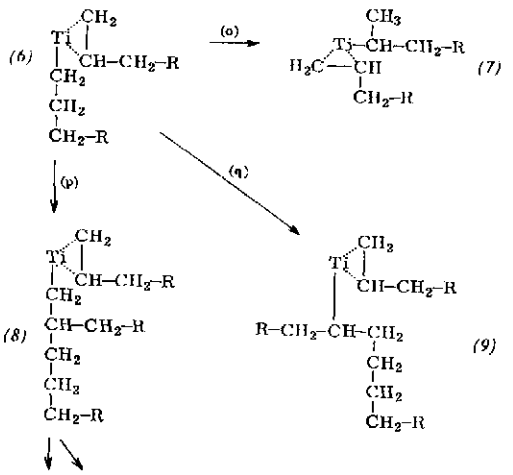


(n)

Introduction of the reverse reaction is necessary because treatment of an α-olefin with ethylene yields not only the direct products of ethylation, but also the corresponding products from higher ethylene homologues of the α-olefin (see [1], Table 7). It is thus possible to attain the transition to the higher ethylene homologues of 1-alkenes from the ethyltitanium-α-olefin complexes in Scheme 1 via the A-reaction.

The processes occurring on oligomerization of the α-olefins are less complicated. Here, however, the isomerization caused by the migration of the double bonds must be taken into consideration. The experimental results indicate that the two processes occur concurrently. Only the primary steps of the reactions need be shown (Scheme 2), since the subsequent course of the reaction is readily apparent.

The olefin complex of the alkyltitanium cation *(6)* formed by the initiation reaction [see Reaction (e)] is trans-



Scheme 2. Initial steps in the double-bond isomerization (o) and the oligomerization (p, q) of α-olefins.

formed irreversibly by three different routes. The preferred direction is chain growth [Reaction (p)], with migration of the alkyl anion to the β-carbon atom of the olefin and formation of *(8)*. The addition of the anion can also proceed to a slight extent in the anti-Markownikoff direction and take place at the α-carbon atom of the olefin, thus yielding *(9)* via Reaction (q). The resulting alkyl group, which is attached to the Ti by a secondary carbon, is especially easy to remove by hydride transfer and displacement, and appears in the products as a straight-chain dimeric olefin with an internal double bond. The location of the double bond becomes fixed by loss of a hydride ion from one of the carbons adjoining the Ti–C bond. The complexed alkyltitanium cation *(8)* formed in step (p) reacts further in a fashion similar to *(6)*. Thus, the next step is chain growth by migration of the anion to the β-carbon atom of the olefin. The slow anti-Markownikoff reaction leads to chain termination. The chain growth reaction is again in competition with the rapid chain transfer to the α-olefin, caused by migration of a hydride ion, a reaction which is typical of this catalyst system and which leads to detachment of the growing chain, thus producing an olefin of the branched vinyl type.

The selective shift of the double bond from the Δ^1- to the Δ^2-position is easily explained by the processes occurring during the transfer of hydride ions from the alkyl chain to the complexed olefin. A constant transfer of hydride to olefin takes place in the starting complex *(6)*, whose alkyl group corresponds to the π-complexed olefin. The hydride transfer to the β-carbon atom of the olefin has no further effect, as the bonding situation remains unchanged. However, the process becomes irreversible when the hydride transfer proceeds via the anti-Markownikoff route to the α-carbon atom of the olefin, with formation of *(7)* and subsequent hydride release from the CH_2 group adjacent to the Ti–C bond. As a result of this back-and-forth migration of hydrides in complexes *(6)* and *(7)*, the double-bond is shifted to the Δ^2-position. The double-bond migration does not proceed further than to the Δ^2-position because the 2-olefins are then rapidly displaced from the π-bond.

7. Experimental

a) Starting Materials

Dimethylaluminum chloride and methylaluminum dichloride were prepared from technical grade methylaluminum sesquichloride by treatment of the latter with sodium chloride or with aluminum chloride; the products were fractionated and analysed for their methyl group and chloride contents [13, 14]. The ethylaluminum compounds were obtained in the same manner.

Methyltitanium trichloride [6, 7] was prepared from titanium tetrachloride and trimethylaluminum, using a method similar to that described by *Karapinka* et al. [15]; it was purified (CH_3–Al content < 0.1 mole-%) and stored at −78 °C (solid CO_2); fresh portions were weighed out for each experiment under dry nitrogen.

"Unstabilized" methylene chloride and chloroform were obtained directly from the manufacturer, shaken with phosphorus pentoxide and then fractionated, discarding the forerun and afterrun (each 10–15 % of total). The distillates were stored and transferred under nitrogen. Other solvents were dried and fractionated by the usual methods and were also stored under nitrogen.

Pure ethylene, propylene, and 1-butene were available (minimum purity > 99.9 %; O_2 < 10 ppm; water < 50 to 100 ppm). The ethylene was freed from traces of water by cooling to −78 °C; the propylene and 1-butene were dried over magnesium perchlorate. The 1-pentene, 1-hexene, 1-heptene, and 1-octene were of 99 % purity, the 1-decene was 98 % pure. The liquid olefins were dried over sodium and stored under nitrogen. The purity of all the olefins was checked by gas chromatography and infrared spectroscopy.

b) Oligomerization of the α-Olefins

Three hundred ml of dry, deaerated methylene chloride and 330 ml of the α-olefin were placed in a 1000-ml flask provided with a stirrer and a low-temperature thermometer. The material in the flask was under a blanket of extra pure nitrogen and moisture was carefully excluded. The mixture was cooled with stirring to −80 °C, using an isopropanol/solid carbon dioxide bath. Then, 15 mmoles of methyltitanium trichloride and 10 mmoles of methylaluminum dichloride, each dissolved in 15 ml of methylene chloride, were added separately to the reaction mixture. The resultant dark red, clear solution was kept at about −70 °C for 15 hours and was then decomposed by addition of 20 ml of methanol. The mixture was left to stand until it had attained room temperature and was washed. It was then divided by distillation into large fractions which were studied by gas chromatography, analysis with chlorosulfonyl isocyanate [16, 17], ozonolysis, or infrared spectroscopy.

c) Quantitative Determination of the Alkyl Groups Attached to Titanium

An absolutely dry and oxygen-free solution of the α-olefin (*e.g.* 1-pentene or 1-octene) in methylene chloride or toluene was cooled to −70 °C with exclusion of air, and a measured

[13] *F. C. Hall* and *A. W. Nash*, J. Instn. Petroleum Technologists *23*, 679 (1937).

[14] *A. v. Grosse* and *I. N. Mavity*, J. org. Chemistry *5*, 108 (1940).

[15] *G. L. Karapinka* et al., J. Polymer Sci. *50*, 143 (1961).

[16] *R. Graf*, Liebigs Ann. Chem. *661*, 111 (1963); German Patent 1112063 (Febr. 8th, 1959), Farbwerke Hoechst AG.

[17] *H. Bestian* et al., Angew. Chem. *74*, 965 (1962); Angew. Chem. internat. Edit. *2*, 41 (1963).

quantity of the test solution of the organometallic compound was then added with stirring. If this solution did not contain alkylaluminum dichloride, the latter had to be added as a catalyst. The mixture was stirred at −70 °C for 15–60 minutes, the dissolved gases were removed by thorough evacuation, and the alkyl groups attached to the aluminum were determined by methanolysis *in vacuo*. The nascent gases were removed by a simple device consisting of a mercury pipette and a burette. The gas mixture was analysed by gas chromatography. The quantity of alkyl groups attached to the Ti and Al of the sample was determined by a blank analysis (without addition of olefin).

d) Examples

α) *Mixture of Methyltitanium Trichloride and Methylaluminum Dichloride*

A solution of 20 ml of 1-pentene in 100 ml of absolute methylene chloride was cooled under nitrogen to −70 °C in a 500-ml flask equipped with a stirrer and dropping funnel; 10 ml of a 0.85 M solution of methylaluminum dichloride and 5 ml of a 0.96 M methyltitanium trichloride solution were then added one after the other. The mixture was stirred for 50 minutes at −70 °C, the stirrer was removed, and the flask stoppered. The flask was then evacuated for 5 minutes by means of an efficient vacuum pump. A total reaction time of 60 minutes was thus attained. Ten ml of methanol were added *in vacuo* to the cold mixture, and the gas evolved while the mixture attained room temperature was carefully pumped off. A solid CO_2/acetone trap placed between the reaction flask and the pump served to retain the major portion of the volatile solvent. The measured quantity of gas was analysed by gas chromatography.

A blank determination of the Al and Ti mixture (without addition of pentene) was also made by decomposition with methanol.

Total methyl content:	13.2 mmoles of CH_4
CH_3-Al content:	8.4 mmoles of CH_4
Difference (CH_3—Ti):	4.8 mmoles of CH_4
For comparison (5 ml of CH_3TiCl_3 solution):	4.8 mmoles of CH_4

β) *Analysis of Methyltitanium Trichloride for CH_3-Al Constituents*

As described in α), 10 ml of the methyltitanium trichloride solution to be tested was treated with 1-pentene in the presence of 10 ml of appr. 1 M ethylaluminum dichloride solution. The chief product of methanolysis is ethane; any methane present indicates the presence of CH_3-Al constitutents in the titanium compound. The purest available preparations of methyltitanium trichloride (aluminum-free according to [15]) gave values of 0.05–0.10 mole-% of unreacted methyl groups, which should be regarded as the blank value of the method or as a small CH_3-Al content in the preparations.

γ) *Stoichiometric Reactions of Olefins with the Mixed Catalyst*

A mixture of 5.5 ml (50 mmoles) of pure titanium tetrachloride and 5.0 ml (50 mmoles) of dimethylaluminum chloride was prepared at room temperature under nitrogen. The vessel used was a 500-ml flask equipped with a stirrer, a dropping funnel, and a 2.5-liter gas measuring vessel. The mixture was diluted with 200 ml of absolute methylene chloride and cooled to about −70 °C; the appropriate quantity of 1-pentene, diluted with 20 ml of methylene chloride, was then added dropwise over a period of an hour at −70 °C. When ethylene was used as the olefin, it was introduced as a gas. Stirring was continued for further 15 minutes and the mixture was then slowly decomposed by dropwise addition of methanol. The mixture was allowed to reach room temperature (+20 °C) The quantity of gas liberated was measured and analysed by gas chromotography. The methylene chloride solution of the reaction products was washed at low temperature and also analysed by gas chromatography.

The authors wish to express their thanks to Dr. H. G. Tennent of the Hercules Powder Company, Wilmington, Del., for valuable discussions of the mechanism of the reaction.

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Isothiazoles [1]

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The ring system of non-anellated 1,2-thiazoles (isothiazoles) has only recently become accessible. Four syntheses and numerous interconversions have opened up new routes to compounds which command interest as intermediates and as analogues of natural products and established pharmaceuticals.

Introduction

Isothiazole and thiazole are related to pyridine in a similar way as thiophene is to benzene. This is particularly apparent in the similarity of their physical properties, including those of their derivatives, and of their odor, but less so in their chemical properties.

Thiazoles and benzoisothiazoles [2–5] have long been known. The idea of replacing the pyridine or thiazole

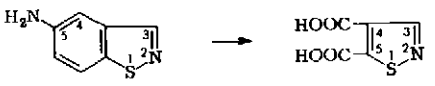
[1] Part 3 of a series on isothiazoles. Part 2: *F. Hübenett* and *Hd. Hofmann*, Angew. Chem. *75*, 420 (1963); Angew. Chem. internat. Edit. *2*, 325 (1963).

[2] *S. Gabriel* and *T. Posner*, Ber. dtsch. chem. Ges. *28*, 1027 (1895).
[3] *S. Gabriel* and *G. Stelzner*, Ber. dtsch. chem. Ges. *29*, 161 (1896).
[4] *K. Fries* and *G. Brothuhn*, Ber. dtsch. chem. Ges. *56*, 1630 (1923).
[5] *R. Stollé*, Ber. dtsch. chem. Ges. *58*, 2095 (1925).

ring in well known pharmaceuticals by the isothiazole nucleus has recently stimulated the development of two syntheses of this heterocyclic ring system. Further routes, which have made isothiozoles readily accessible, were published shortly afterwards.

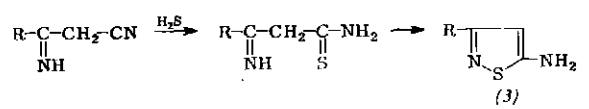
I. Syntheses

Adams and *Slack* [6] first prepared isothiazole in 1956; their synthesis started with *o*-chlorobenzaldehyde and involved thirteen stages. Significant intermediates are 5-aminobenzoisothiazole *(1)* and 4,5-isothiazoledicarboxylic acid *(2)*, which is obtained from *(1)* by oxidation. This classical route, though remarkable for its elegance, hardly lends itself to industrial application and development.



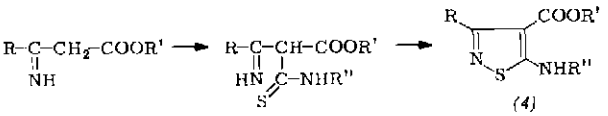
(1) *(2)*

These authors also provided the first account of some aspects of the chemistry of isothiazole [7] and reported a simpler synthesis for 3-substituted 5-aminoisothiazoles, which has already found industrial application [8]. The starting materials for this synthesis are aliphatic β-imino nitriles, which are converted by addition of H_2S to β-imino thioamides, and then by oxidative cyclization into 3-alkyl-5-aminoisothiazoles *(3)*.



(3)

Goerdeler and co-workers [9–13] independently employed a similar method for building up the isothiazole skeleton, and varied it in a number of ways. Thus, by starting with β-imino esters and isothiocyanates, they obtained 3-alkyl-4-alkoxycarbonyl-5-aminoisothiazoles *(4)*.

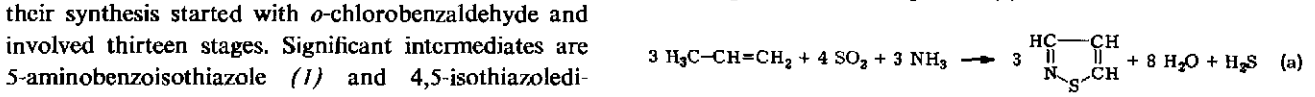


(4)

By oxidative cyclization of suitable open-chain compounds, they achieved the first preparation of isothiazoles incorporating hydroxyl, alkoxyl, and amino groups in the 3-position [13].

Another synthesis, developed by us [14], starts with easily accessible cheap olefins and is capable of yielding isothiazole and its 3-, 4-, or 5-substituted alkyl and aryl derivatives.

Since toluene or *p*-xylene can be converted into benzonitrile or terephthalodinitrile [15–17] in a gaseous catalytic reaction with sulfur dioxide and ammonia, we expected to obtain acrylonitrile in an analogous reaction involving propylene. However, the reaction proceeds differently with olefins, occurring with propylene according to the overall equation (a).



(a)

This reaction is applicable to olefins with three or more carbon atoms. Suitable catalysts are activated alumina or silica gel containing oxides of aluminum, titanium, zirconium, or other multivalent metals. At 300–350 °C, yields of 25–65% are obtained depending on the olefin used. Isobutylene yields 4-methylisothiazole, 1-butene or 2-butene yield mixtures of 3- and 5-methylisothiazole [18–22], α-methylstyrene affords 4-phenylisothiazole, and both β-methylstyrene and allylbenzene give 5-phenylisothiazole [1]. If, as in the case of butene, a thiophene ring can be formed, it is usually obtained in a side-reaction, so that the yields of the isothiazoles are lower. Pentenes, for example, yield more methylthiophene than ethyl- and dimethylisothiazoles.

Isothiazoles are also formed by interaction of acetylenes or alcohols with sulfur dioxide and ammonia; thus, methylacetylene gives rise to isothiazole, and isobutanol to 4-methylisothiazole [20].

A further synthesis, yielding not only isothiazole and its 3-alkyl derivatives [23], but also the corresponding isoselenazoles [24], was described by *Wille* and his coworkers. The synthesis employs aldehydes or ketones

[6] *A. Adams* and *R. Slack*, Chem. and Indust., *1956*, 1232; Chem. Abstr. *51*, 5050 (1957).

[7] *A. Adams* and *R. Slack*, J. chem. Soc. (London), *1959*, 3061.

[8] Bidizole, Sulphonamide Therapy. Pamphlet by May & Baker Ltd., Dagenham, England (November 1961).

[9] *J. Goerdeler* and *H. W. Pohland*, Angew. Chem. *72*, 77 (1960).

[10] *J. Goerdeler* and *H. W. Pohland*, Chem. Ber. *94*, 2950 (1961).

[11] *J. Goerdeler*, Angew. Chem. *74*, 498 (1962).

[12] *J. Goerdeler* and *H. W. Pohland*, Chem. Ber. *96*, 526 (1963).

[13] *J. Goerdeler* and *W. Mittler*, Chem. Ber. *96*, 944 (1963).

[14] German Patent Application Z 9032 IV d/12p (Oct. 26th 1961); *H. J. Zimmer*; inventors: *F. Hübenett*, *F. H. Flock*, and *Hd. Hofmann*.

[15] German Patent Application Z 8871 IV b/12o (July 22nd, 1961) H. J. Zimmer; inventors: *F. Hübenett*, *F. H. Flock*, and *H. Rempfer*.

[16] German Patent Application Z 9392 IV b/12o (May 4th, 1962) H. J. Zimmer; inventors: *F. Hübenett*, *F. H. Flock*, and *Hd. Hofmann*.

[17] German Patent Application Z 9393 IV b/12o (May 4th, 1962) H. J. Zimmer; inventors: *F. Hübenett*, *F. H. Flock*, and *Hd. Hofmann*.

[18] *F. Hübenett*, *F. H. Flock*, and *Hd. Hofmann*, Angew. Chem. *74*, 653 (1962); Angew. Chem. internat. Edit. *1*, 508 (1962).

[19] German Patent Application Z 9388 IV d/12p (May 4th, 1962) H. J. Zimmer; inventors: *F. Hübenett*, *F. H. Flock*, and *Hd. Hofmann*.

[20] German Patent Application Z 9389 IV d/12p (May 4th, 1962) H. J. Zimmer; inventors: *F. Hübenett*, *F. H. Flock*, and *Hd. Hofmann*.

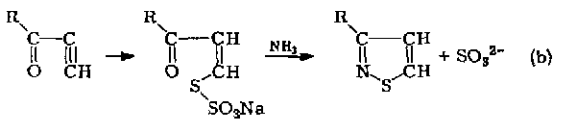
[21] German Patent Application Z 9390 IV d/12p (May 4th, 1962) H. J. Zimmer; inventors: *F. Hübenett*, *F. H. Flock*, and *Hd. Hofmann*.

[22] German Patent Application Z 9391 IV d/12p (May 4th, 1962) H. J. Zimmer; inventors: *F. Hübenett*, *F. H. Flock*, and *Hd. Hofmann*.

[23] *F. Wille*, *L. Capeller*, and *A. Steiner*, Angew. Chem. *74*, 467 (1962); Angew. Chem. internat. Edit. *1*, 335 (1962).

[24] *F. Wille*, *A. Ascherl*, *G. Kaupp*, and *L. Capeller*, Angew. Chem. *74*, 753 (1962); Angew. Chem. internat. Edit. *1*, 553 (1962).

incorporating α-triple bonds (ethynyl ketones). Addition of thiosulfate, thiocyanic acid, or selenocyanic acid, followed by elimination of sulfurous or hydrocyanic acid in liquid ammonia results in cyclization to 1,2-thiazoles or 1,2-selenazoles, respectively [Reaction (b)].



The above syntheses have made isothiazoles an interesting class of compounds, encompassing a large number of accessible derivatives. Each of the syntheses has its special merits, *e.g.* 5-amino- and 3-hydroxy- or 3-alkoxy derivatives are only obtainable by *Adams* and *Slack*'s or *Goerdeler*'s methods.

The significance of our synthesis appears to be its versatility, the simplicity of the starting materials, and the fact that large-scale production costs should be below those for comparable pyridine analogues.

II. The Course of the Synthesis from Olefins

Our original assumption that olefins, in common with toluene, for example, form nitriles as the first step [15–17], and that successive addition of hydrogen sulfide, and the oxidizing action of sulfur dioxide or sulfur results in cyclization, is not correct. Experiments employing acrolein or acrylonitrile provided no evidence of isothiazole formation; on the above assumption, methacrylonitrile should have yielded 4-methylisothiazole, but we obtained only 4-cyanoisothiazole in low yield (10%), so that a route involving aldehydes or nitriles must be discounted.

An indication of the course of the reaction is provided by the observation that n-butenes invariably give mixtures of 3- and 5-methylisothiazoles, while both allylbenzene and β-methylstyrene yield exclusively 5-phenylisothiazole. Thus, butenes appear to react as an equilibrium mixture of isomers, whilst the phenyl derivative appears to have the equilibrium displaced largely towards the β-methylstyrene form, owing to conjugation effects. It must therefore be assumed that the nitrogen enters in the allyl position, while sulfur is added at the double bond; in other words, a reactive sulfur-nitrogen compound is first formed, possibly a thionyl imide or one of its isomers [25].

In the meantime, *Olofson* and his co-workers [26] have succeeded in synthetizing isothiazole by a new route, which proceeds by way of trithiones and dithiolium salts. Here, unsymmetric dithiolium salts react preferentially in one direction; our synthesis may therefore proceed via analogous sulfur heterocyclics.

III. Properties

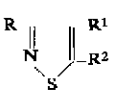
Isothiazole and its methyl derivatives are colorless neutral liquids, with a characteristic odor reminiscent of pyridine, and high solubility properties. They are miscible in all proportions with the common solvents except water. The physical properties of the new isothiazole derivatives, prepared by us, are summarized in Tables 1 and 2.

Table 1. Solubility, density, and refractive index of some isothiazole derivatives at 20 °C.

	Solubility [w/w %] of water	Solubility [w/w %] in water	d_4^{20}	n_D^{20}
Isothiazole	6.6	3.4	1.1706	1.5324
3-Methylisothiazole	6.6	3.6	1.0924	1.5209
4-Methylisothiazole	2.5	1.8	1.0866	1.5248
5-Methylisothiazole	7.0	3.2	1.1060	1.5212

A large number of further isothiazole derivatives is described elsewhere [7, 10–13] [*]. Our Tables also include derivatives that were previously described, because we believe the larger quantities of products now prepared allowed more accurate determination of their physical properties.

Table 2. Melting points and boiling points of some isothiazole derivatives.



R	R1	R2	m.p. [°C]	b.p. [°C/mm]
—H	—H	—H		115/760 [7]
—CH_3	—H	—H		134/760 [7]
—H	—CH_3	—H		146/760
—H	—H	—CH_3		142.5/760
—H	—C_6H_5	—H	36–37	
—H	—H	—C_6H_5	44–45	
—H	—CN	—H	87	
—H	—NO_2	—H	87	
—CH_3	—NO_2	—H	3	103/10 [7]
—H	—NO_2	—CH_3	36	99/9

[25] *M. Becke-Goehring*, Z. anorg. Chem. *268*, 47 (1952).

[26] *R. A. Olofson*, Harvard University, personal communication (1963).

[*] Note added in proof: Meanwhile the following papers have been published: *D. Buttimor, D. H. Jones, R. Slack*, and *K. R. H. Wooldridge*, J. chem. Soc. (London) *1963*, 2032; *J. Goerdeler* and *H. Horn*, Chem. Ber. *96*, 1551 (1963).

Table 2 (Continued).

R	R^1	R^2	m.p. [°C]	b.p. [°C/mm]
—H	—CH=CH—NO_2	—H	139—140	
—H	—NH_2	—CH_3	84—85	41—143/20
—H	—NH—CO—CH_3	—CH_3	93	
—H	—CH=CH—COOH	—H	190—191	
—H	—CH=C(N=C(O)—C_6H_5)—C=O	—H	212	
—H	—CHO	—H	58	
—H	—SO_3H	—H	262 (decomp.)	
—H	—SO_2Cl	—H	63	128/15
—H	—SO_2NH_2	—H	96—97	
—CH_3	—SO_3H	—H	278 (decomp.)	
—CH_3	—SO_2Cl	—H		130/15
—CH_3	—SO_2NH_2	—H	77—78	
—H	—SO_3H	—CH_3	236 (decomp.)	
—H	—SO_2Cl	—CH_3	6	133/15
—H	—SO_2NH_2	—CH_3	111—112	
—H	—CH_3	—SO_3H	266	
—H	—CH_3	—SO_2Cl		120/15
H	—CH_3	—SO_2NH_2	118	
—CH_3	—CH_3	—H		168/750
—H	—CH_3	—CH_3		171/750
—H	—H	—CH=CH—C_6H_4—*m*—NO_2	160—161	
—H	—CH_3	—CH=CH—C_6H_4—*m*—NO_2	113.5—114	
—H	—NO_2	—CH=CH—C_6H_4—*m*—NO_2	194—196	
—H	—NO_2	—CH=CH—C_6H_5	97—98	
—H	—Cl	—H		145/760
—CH_3	—Cl	—H		160/760
—H	—Cl	—CH_3		164/760
—H	CH_2Cl	—H		100/200
—Cl	—CH_3	—H		188/760
—H	—Br	—H	32	88—91/48
—CH_3	—Br	—H	32	183/760

Examination of the toxicity of isothiazole, 4-methylisothiazole, and isothiazole-4-carboxylic acid using white mice and rats [27] shows that isothiazole is 10—15 times as toxic as pyridine, while 4-methylisothiazole possesses only about 25% of the toxicity of isothiazole (Table 3). Since isothiazole-4-carboxylic acid is even less toxic, the assumption seems justified that the methyl derivative is oxidized *in vivo* to the acid.

Groups of white rats (body weight 170–210 g) received geometrically increasing doses of the above compounds dissolved in 20% Tween 20 orally or intraperitoneally (5 ml per kg body weight). The LD 50 (lethal dose for 50% of the experimental animals) was determined 48 hours later and was calculated according to the method of *Litchfield* and *Wilcoxon* [28]. The figures in brackets show the distribution, with 19/20 probability. Other rats received a daily dose of 20 mg/kg body weight of pyridine, isothiazole, or 4-methylisothiazole over a period of 10 days. No obvious toxic effects were observed, so that small subtoxic doses appear to be without cumulative effect [27].

Table 3. Comparison of the acute toxicity of isothiazole, 4-methylisothiazole, isothiazole-4-carboxylic acid, and pyridine [27].

	LD 50 [mg/kg]	
	oral	intraperitoneal
Isothiazole	81 (46—125)	53 (31—82)
4-Methylisothiazole	280 (195—405)	255 (210—340)
Isothiazole-4-carboxylic acid	>800	>800
Pyridine	1450 (1300—1630)	562 (465—680)

[27] *P. Holtz* and *E. Westermann*, Pharmacological Institute University Frankfurt/Main.

[28] *J. P. Litchfield* and *F. Wilcoxon*, J. Pharmakol. exp. Therap. 96, 99 (1949).

IV. Reactions

The publication of *Adams* and *Slack* [7] gave some indication of certain chemical properties of the isothiazoles, and we have continued investigations in this direction. Thus it is found that 3- and 5-carboxyl groups in isothiazole are readily decarboxylated, whereas isothiazole-4-carboxylic acid is remarkably stable.

4-Methylisothiazole may be oxidized by air in the gaseous phase in the presence of water-vapor to give mixtures of isothiazole-4-carboxaldehyde and -4-carboxylic acid [29]. However, 3- and 5-methylisothiazole gave only isothiazole as the main product owing to decarboxylation of the intermediate acids. 3-Methylisothiazole also affords small yields of a very unstable by-product (m.p. 25–30 °C), whose odor resembles that of benzaldehyde, and which reduces ammoniacal solutions of silver salts; it is thus presumably isothiazole-3-carboxaldehyde.

Isothiazole-4-carboxaldehyde possesses an odor of bitter almonds, and gives the usual aldehyde reactions; it condenses with nitromethane to yield 1-isothiazol-4-yl-2-nitroethylene and reacts with malonic ester to form β-isothiazol-4-ylacrylic acid.

The reactivity of the methyl groups depends on their position on the isothiazole nucleus. Certain condensation reactions occur with 5-methylisothiazole, but not with the 3- or 4-methyl derivatives. Indeed, the reactivity of

[29] German Patent Application Z 9808 IV d/12p (Dec. 7th, 1962) H. J. Zimmer; inventors: *F. Hübenett*, *Hd. Hofmann*, and *S. Füllert*.

the methyl group at the 5-position is not particularly striking; condensation with benzaldehyde does not occur, and interaction with 3-nitrobenzaldehyde results in 1-isothiazol-5-yl-2-(3′-nitrophenyl)ethylene. The activity of the 5-methyl group may be increased by the introduction of a nitro group at the 4-position, thus making the condensation with benzaldehyde possible. Reaction with formaldehyde gave resinous products.

Isothiazoles behave variously towards oxidizing agents. All attempts to obtain amine- or sulfoxides by the action of hydrogen peroxide invariably resulted in destruction of the ring; ammonium sulfate is found amongst the reaction products. In contrast, isothiazoles are fairly stable towards potassium permanganate, a fact that was utilized by *Adams* and *Slack* [6] in their first synthesis of isothiazole-4,5-dicarboxylic acid, and by ourselves in the proof of the structure of 4-methylisothiazole by its oxidation to the known 4-carboxylic acid. Chromic acid can also be used to oxidize methyl groups of isothiazoles.

It is thus surprising that isothiazole is largely recovered unchanged after several days' treatment with nitric acid/sulfuric acid mixtures at 150 °C but, when care is taken to have a minimum of 1 mole of sulfur trioxide present throughout, nitration proceeds readily in yields of up to 90% [30]. The nitro group invariably enters at the 4-position; therefore, 4-methylisothiazole cannot be nitrated.

Similar observations are made in the sulfonation. In the presence of excess sulfur trioxide, the sulfonyl group enters at the 4-position, the yields approaching 90% [31]. In contrast to nitration, it is possible to obtain a sulfonic acid from 4-methylisothiazole although only in low yield. From evaluation of the nuclear magnetic resonance spectra it seems probable, that this is the 5-sulfonic acid [32].

Chlorination and bromination similarly result in preferential substitution at the 4-position [33]; however, the reaction products always contain other halogeno derivatives. Thus, chlorination of isothiazole results in 30–40% yields of 4-chloroisothiazole, but gas-chromatographic examination shows the presence of four additional chlorinated products, including dichloro derivatives, in yields of 3–7%. During halogenation, substitution may also occur in the side-chain. Thus by chlorinating 4-methylisothiazole with irradiation approximately equal quantities of the 3-chloro and 4-chloromethyl derivatives are formed.

The constitution of the 4-halogenoisothiazoles which are isolated as the main products follows from their infrared spectra, which contain strong bands at 855 ± 2 cm^{-1} and 782 ± 5 cm^{-1}; such bands occur in the spectra of all the 4-substituted derivatives but are absent in the spectra of any other derivatives. Furthermore, 4-halogenoisothiazoles cannot be nitrated, whereas 3-methyl-5-bromoisothiazole is readily converted into the 4-nitro derivative [7]. Products that are chlorinated in the side-chain form quaternary salts with pyridine; furthermore the chlorine may be removed by boiling with alcoholic sodium hydroxide and thus estimated.

We performed the halogenations generally above 100°C, but *Goerdeler* [13] succeeded in brominating 3-hydroxy-, 3-alkoxy-, or 3-aminoisothiazole in almost theoretical yields in acetic acid/water at room temperature. Unfortunately this method cannot be extended to isothiazole or its methyl derivatives; at room temperature, the extent of the halogenation is negligible even after several days. At reflux temperatures, however, under otherwise identical conditions, we obtained the 4-bromo derivative from 3-methylisothiazole in almost 80% yield within 5 hours from a total conversion of 88%; 4-bromoisothiazole was obtainable in less than 20% yield only from an overall conversion of 56%.

Isothiazoles react with strong acids or Lewis acids (*e.g.* SO_3) in a molar ratio of 1:1 to form definite adducts. Quaternizations do actually occur but proceed distinctly more slowly than those involving pyridine. We have prepared adducts from isothiazole and methyl iodide (m.p. 149 °C) or ethyl iodide (m.p. 103 °C), and from 4-methylisothiazole and methyl iodide (m.p. 121 °C).

As expected, hydrogenation of the isothiazole ring readily results in ring cleavage. But nitro derivatives of isothiazoles may be reduced to the amines under mild conditions, *e.g.* using ferrous salts in ethanolic ammonia, or iron/hydrochloric acid in the cold.

Amino groups in the 4- and 5-positions show the usual reactions of aromatic amines. Thus, they may be diazotized and coupled to yield dyes. It is noteworthy that 3-aminoisothiazoles behave differently on diazotization: 3-amino-5-phenylisothiazole, like aliphatic amines, yields the 3-hydroxy compound as major product [13]. The aminoisothiazoles may be monoacetylated.

The 3-hydroxyisothiazoles, which were first described by *Goerdeler* [13], unlike the pyridones, appear to exist predominantly in the enol form and to be very sensitive toward hydrogenation and oxidation. They give a red coloration with ferric chloride and are more acidic than 2-hydroxypyridine and phenol [13].

V. Potential Applications

In the short time that has elapsed since the appearance of the first paper dealing with isothiazole, one derivative is already being produced industrially. This is the sulfonamide made from 3-methyl-5-aminoisothiazole and *p*-aminobenzenesulfonic acid and is marketed under the trade name Bidizole® [8].

Because of the similarity of pyridine and isothiazole derivatives, isothiazoles should be useful primarily in the synthesis of analogues of known pharmaceuticals and natural products. Thus, it might be worth studying more closely the 4-aminoisothiazole analogues of Sulfathiazole® and Sulfapyridine®, or the corresponding derivatives of the 3- and 5-methyl-4-aminoisothiazoles, which our synthesis has made available for the first time or more readily. Compounds like isothiazolylalanine or isothiazolylethylamine, whose preparation from the readily available isothiazole-4-carboxaldehyde should present no difficulties, are structurally related to histidine

[30] German Patent Application Z 9634 IV d/12p (Sept. 1st, 1962) H. J. Zimmer; inventors: *F. Hübenett* and *H. Heinze*.

[31] German Patent Application Z 9956 IV d/12p (March 5th, 1963) H. J. Zimmer; inventors: *F. Hübenett* and *H. Heinze*.

[32] *A. Mannschreck*, personal communication.

[33] German Patent Application Z 10205 IV d/12p (July 1st, 1963) H. J. Zimmer; inventors: *F. Hübenett* and *H. Heinze*.

and histamine. A study of the action of isothiazole derivatives that are related to active natural products on the metabolism of normal and degenerated cells should lead to significant results. The relationship of isothiazolecarboxylic acids to nicotinic and isonicotinic acid should prompt pharmaceutical examination of isothiazolecarbohydrazides.

Dyes derived from isothiazole are obtainable both by diazotization (*e.g.* of the 4-amino compounds) and by condensation with azomethines, for which purpose 5-methylisothiazole, isothiazole-4-carboxaldehyde, and the amino derivatives should be particularly suitable.

Isothiazole and its methyl derivatives, particularly the 4-methyl isomer, are excellent solvents. Inorganic salts, such as $Co(NO_3)_2 \cdot 6H_2O$, $FeCl_3 \cdot 6H_2O$, and $ZnCl_2$ are soluble in isothiazole. The distribution coefficient for phenol between 4-methylisothiazole and water is approximately 50, that for pyridine/water is 5. Since isothiazoles form azeotropes with water and can readily be separated when a derivative of suitable boiling point is selected, they are good extracting agents [34].

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German version: Angew. Chem. *75*, 1189 (1963)

[34] German Patent Application Z 9394 IV b/12o (May 4th, 1962) H. J. Zimmer; inventors: *F. Hübenett* and *H. Heinze*.

Type and Extent of Isomerization of Straight-Chain Mono-olefins during the Koch Carboxylic Acid Synthesis [1]

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Dedicated to Professor Dr. Karl Ziegler on the occasion of his 65th birthday

When straight-chain mono-olefins, from pentene to decene, are subjected to the Koch carboxylic acid synthesis by the addition of CO and H_2O or CH_3OH in the presence of strongly acidic catalysts, not only the expected secondary acids, but also mixtures of a specific type of tertiary acids or their methyl esters are formed. When the catalysts contain boron trifluoride, the secondary acids are formed in ratios of isomers which are, within the scope of this investigation, independent of the experimental conditions and which agree well with the values calculated from the isomer equilibria of the corresponding n-olefins. Using concentrated sulfuric acid as catalyst, a larger proportion of tertiary acids is obtained than with BF_3-catalysis, and amongst the secondary acids, those isomers predominate in which the COOH group is situated near the centre of the molecule.

I. Introduction

The isomerization of straight-chain olefins has been extensively investigated because of its importance in many chemical reactions; both the ordinary shift of the double bond and the rearrangement of the carbon skeleton have been studied [2]. For reactions which take place in the presence of acidic catalysts, it is generally agreed that the formation of carbonium ions [3] can be assumed to be the first reaction step. Opinions differ, however, concerning the rearrangement of these carbonium ions. It is well established that these rearrangements take place very rapidly, that they do not require much energy, and that the formation of the most stable ions is preferred [4]. It can be assumed that, in the presence of strongly acidic catalysts, the carbonium ions are already in a state of equilibrium which (at least in the double-bond shift of straight-chain olefins) can be regarded as a first step towards the attainment of the isomerization equilibrium.

II. The Koch Carboxylic Acid Synthesis

It is difficult to determine such an equilibrium even approximately quantitatively, as the presence of strongly acidic catalysts (*e.g.* conc. sulfuric acid) gives rise to a certain amount of side reactions, such as chain-splitting and polymerization. However, it is possible to study the intermediates which take part in the equilibrium by subjecting the olefins to the Koch carboxylic acid synthesis [5]. By this procedure the olefins are converted to the corresponding carboxylic acids by addition of carbon monoxide and water in the presence of strongly acidic catalysts. This also allows a quantitative

[1] Reported in part at the meeting of the Gesellschaft Deutscher Chemiker, Aachen 1961; Angew. Chem. *73*, 767 (1961).

[2] *G. Collin*, Ph. D. Thesis, Technische Hochschule Aachen, 1961; *F. Asinger, B. Fell*, and *G. Collin*, Chem. Ber. *96*, 716 (1963).

[3] *L. Schmerling*, Ind. Engng. Chem. *45*, 1447 (1953).

[4] *J. Hine*: Physical Organic Chemistry. McGraw-Hill, New York 1956.

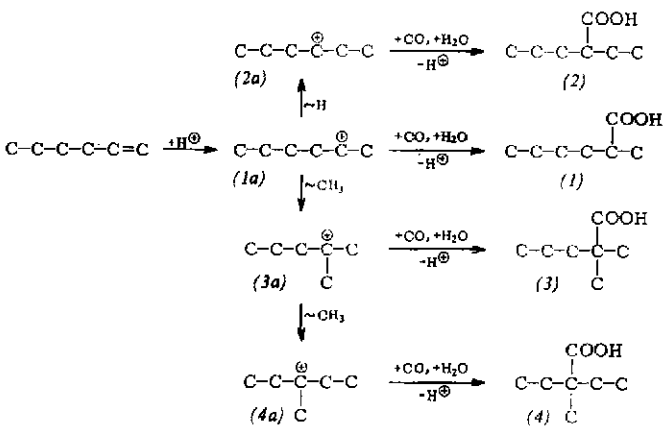
[5] *H. Koch*, Brennstoff-Chem. *36*, 321 (1955); Fette, Seifen, Anstrichmittel *59*, 493 (1957).

determination to be made of the extent of rearrangement in the carbon skeleton of n-olefins, since in addition to the expected secondary acids, varying amounts (governed by the conditions of the reaction) of tertiary acids of a special type are formed, *e.g.* 2-methylalkane-2-carboxylic acids, 3-methylalkane-3-carboxylic acids, *etc.* On the other hand, no straight-chain carboxylic acids are formed which would arise by the addition of carbon monoxide and water onto the terminal carbon atom. This means that the reaction strictly obeys the Markownikoff rule.

The number of possible isomeric carboxylic acids (Z) is given by the simple relationship

$$Z = N-2$$

where N = the number of carbon atoms in the olefin. Applied to n-Δ^1-hexene, a calculation gives Z = 4, corresponding to the four isomeric C_7-acids (hexane-2-carboxylic acid *(1)* and hexane-3-carboxylic acid *(2)* as secondary, and 2-methylpentane-2-carboxylic acid *(3)* and 3-methylpentane-3-carboxylic acid *(4)* as tertiary acids).



No other isomers are formed, because the rearrangement of the carbon skeleton is confined to the formation of tertiary carbonium ions of the type *(3a)* and *(4a)*, *i.e.* those with a methyl group at the point of branching, as intermediates.

III. Reaction Conditions and Catalysts

The extent to which tertiary acids are formed depends upon the reaction conditions. The synthesis gives the best results at −20 to +80 °C, at CO-pressures of 20 to 100 atm, and with the following catalysts:

Conc. sulfuric acid
Hydrofluoric acid by itself or in combination with BF_3
$H[BF_3OH]$ (monohydroxofluoroboric acid)
$[H_3O][BF_3OH] = BF_3{\cdot}2\,H_2O$ (hydronium monohydroxofluoroborate)
BF_3/H_2SO_4
BF_3/H_3PO_4
Conc. H_3PO_4 (~95%).

When the addition of carbon monoxide has finished and water has been added in stoichiometric proportions, the carboxylic acids are obtained in average yields of 85 to 95%, based on the olefins. On addition of alcohol instead of water, using conc. H_2SO_4 or $BF_3{\cdot}H_2O$ as catalysts, the esters are formed. This process has also been described recently by Russian authors [6].

With alkoxofluoroboric acids, *e.g.* $BF_3{\cdot}CH_3OH$, $BF_3{\cdot}C_2H_5OH$, and $BF_3{\cdot}$n-C_3H_7OH [7] as catalysts, the esters [8] are obtained almost quantitatively under the same mild conditions. Even if water is added after the CO-addition, practically only the esters are obtained, because the BF_3, on account of its stronger affinity for water, absorbs the water and leaves the alcohol to the acyl ion.

IV. Analysis of the Reaction Products

Alkoxofluoroboric acids offer some advantages as catalysts, particularly for the examination of the extent of isomerization. Here the reaction product remains in homogeneous solution with excess catalyst, whereas this is only occasionally the case when purely inorganic catalysts are used. Furthermore, analysis of the mixture of acids is easier when they are present as their esters. By means of capillary-column vapor phase chromatography it is possible to separate the mixtures of isomers up to and including the C_{12}-acids in the form of their methyl esters and to analyse them quantitatively. The fractions were characterized by comparison with model substances which had been prepared by known procedures.

V. Composition of the Isomer Mixtures

1. The Relative Amounts of Tertiary and Secondary Acids

Starting from straight-chain Δ^1-olefins from hexene to decene, with conc. H_2SO_4 or $BF_3{\cdot}CH_3OH$ as catalyst and at constant CO-pressure (100 atm), the proportion of tertiary acids increases significantly on raising the temperature from −5 to +15 °C. In the presence of

Table 1. Temperature-dependence of the relative amounts of tertiary and secondary acids. CO-pressure: 100 atm.

Olefin	H_2SO_4 (96 %)				$BF_3{\cdot}CH_3OH$			
	tert. acids [%]		sec. acids [%]		tert. acids [%]		sec. acids [%]	
	−5 °C	+15 °C	−5 °C	+15°C	−5 °C	+15 °C	−5 °C	+15°C
1-hexene	43	58	57	42	22	35	78	65
1-heptene	54	68	46	32	26	42	74	58
1-octene	50	64	50	36	30	43	70	57
1-nonene					34	44	66	56
1-decene					33	50	67	50

[6] *K. V. Puzitskii, Ya. T. Eidus,* and *K. G. Ryabova,* Dokl. Akad. Nauk SSSR *141*, 636 (1961).

[7] German Pat. 1064941 (March 3rd, 1960), Studiengesellschaft Kohle mbH, Mülheim/Ruhr, inventors: *H. Koch* and *K. E. Möller.*

[8] German Pat. 1085143 (July 14th, 1960), Chemische Werke Bergkamen AG, inventors: *G. Rohlffs* and *S. Pawlenko.*

H_2SO_4 as catalyst, a stronger tendency exists toward rearrangement of the carbon skeleton leading to the formation of tertiary acids (Table 1).

It was known [9] that the formation of tertiary acids can be largely suppressed by raising the CO-pressure. However, this influence of the pressure decreases above a certain temperature depending on the type of olefin used.

2. Ratio of the Isomers of the Secondary Acids

a) *Catalysts Containing Boron Trifluoride*

The relative amounts of isomeric secondary acids which are formed from 1-olefins in the presence of catalysts containing BF_3 are independent of the temperature and the CO-pressure between −5 and +15 °C. The position of the double bond in the n-olefins investigated is also without influence. Thus 2-pentene, 2-hexene, 3-hexene, 2-heptene, and 3-heptene yield secondary acids with the same ratio of isomers as the corresponding Δ^1-olefins (Table 2).

A survey of calculated values for the composition of the equilibrium mixtures of n-olefin isomers with 4–9 C-atoms at 190 °C was published by *Koch* and *Richter* [10] in 1944. We have compared the ratios of secondary carboxylic acids to be expected from these figures with the values found in our experiments (Fig. 1).

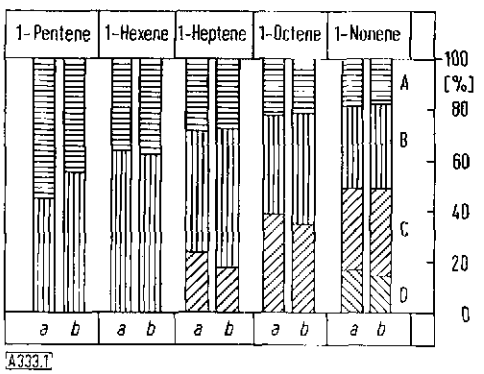


Fig. 1. Ratios of the methyl esters of isomeric secondary carboxylic acids obtained from n-Δ^1-olefins.

(a) Values calculated according to *Koch* and *Richter* [10]

(b) Our own experimental figures.

A = Alkane-2-carboxylic acids
B = Alkane-3-carboxylic acids
C = Alkane-4-carboxylic acids
D = Alkane-5-carboxylic acids

Apart from a slightly larger discrepancy for the C_5-olefin, the calculated and experimental values for the isomer ratios agree well. In the presence of other catalysts containing borofluoride, *e.g.* $BF_3 \cdot C_3H_7OH$, $BF_3 \cdot H_2O$, and $BF_3 \cdot 2H_2O$, under comparable conditions, the same ratio of isomers is obtained, too. It appears that in the presence of these catalysts, equilibria amongst the carbonium ions initially formed are stabilized by the subsequent reaction with CO and H_2O or CH_3OH.

Table 2. Influence of the catalyst on the isomer ratio of secondary carboxylic acids. CO-pressure: 100 atm, temperature: + 15 °C.

Olefin	-carboxylic acid	Isomers [%] Catalyst contg. BF_3	Catalyst H_2SO_4 (96 %)
1-Hexene	Hexane-2-	36.5	30.3
	Hexane-3-	63.5	69.7
1-Heptene	Heptane-2-	25.4	17.4
	Heptane-3-	56.3	64.6
	Heptane-4-	18.3	18.0
1-Octene	Octane-2-	20.5	14.4
	Octane-3-	43.9	44.8
	Octane-4-	35.6	40.7
1-Nonene	Nonane-2-	14.5	5.2
	Nonane-3-	35.2	36.2
	Nonane-4-	36.2	35.0
	Nonane-5-	14.1	23.6
1-Decene	Decane-2-	14.8	7.9
	Decane-3-	30.2	30.2
	Decane-4-	26.7	28.2
	Decane-5-	28.3	33.6

b) *Sulfuric Acid as Catalyst*

With concentrated sulfuric acid as catalyst, the isomer ratios diverge from those obtained with catalysts containing boron fluoride as the number of carbon atoms in the olefin increases. Secondary acids in which the carboxyl group is nearer to the centre of the molecule are preferred to the alkane-2-carboxylic acids (Table 2).

Table 3 shows, using 1-hexene as an example, that the isomer distribution is independent of the concentration of the acid between 90 and 101 %.

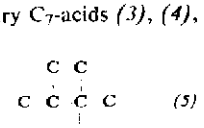
Table 3. Relative amounts of the two secondary C_7-acids depending on the concentration of the sulfuric acid catalyst. Olefine: 1-hexene, CO-pressure: 100 atm; temperature: + 15 °C.

Catalyst	Hexane-3-carboxylic acid [%]	Hexane-2-carboxylic acid [%]
H_2SO_4 (90.4 %)	68.5	31.5
H_2SO_4 (93.7 %)	69.3	30.7
H_2SO_4 (96.0 %)	69.7	30.3
H_2SO_4 (101.1 %)	69.4	30.6

3. Ratio of the Isomeric Tertiary Acids

The formation of tertiary acids cannot be entirely suppressed, even by working at low temperatures (below 0 °C) and high CO-pressures (up to 500 atm). The origin of their formation is a rearrangement of the carbon skeleton to branched carbonium ions of the types *(3a)* and *(4a)*. Further rearrangement of the tertiary acids does not occur under the conditions of the Koch carboxylic acid synthesis.

Some rearrangement does, however, take place in the absence of CO. *Lundeen* [11] showed that 3-methylpentane-3-carboxylic acid rearranges in the presence of conc. H_2SO_4 to a mixture of the three isomeric tertiary C_7-acids *(3)*, *(4)*, and *(5)*.



(5)

[9] *K. E. Möller*, Ph. D. Thesis, Technische Hochschule Aachen, 1954.

[10] *H. Koch* and *H. Richter*, Oel u. Kohle *40*, 231 (1944).

[11] *A. Lundeen*, J. Amer. chem. Soc. *82*, 3228 (1960).

Using the tertiary carboxylic acids formed from 1-hexene as an example, Table 4 shows that the same isomer ratio always occurs with catalysts containing boron fluoride. Within the temperature range investigated (−5 to +15 °C), the ratio is independent of the temperature and duration of the reaction and the CO-pressure. Varying concentrations of sulfuric acid, on the other hand, give rise to different isomer ratios (Table 4). This differs from the results for the secondary acids (Table 2).

Table 4. Influence of the catalyst on the ratio of isomers of the tertiary C_7-acids. Olefin: 1-hexene; CO-pressure: 100 atm; temperature: +15 °C.

Catalyst	2-Methylpentane-2-carboxylic acid [%]	3-Methylpentane-3-carboxylic acid [%]
$BF_3 \cdot CH_3OH$	65.6	34.4
$BF_3 \cdot C_3H_7OH$	65.8	34.2
$BF_3 \cdot H_2O$	63.8	36.2
$BF_3 \cdot 2H_2O$	63.3	36.7
H_2SO_4 (84.6 %)	55.0	45.0
H_2SO_4 (90.4 %)	57.7	42.3
H_2SO_4 (93.7 %)	58.8	41.2
H_2SO_4 (96.0 %)	59.8	40.2
H_2SO_4 (101.1 %)	76.4	23.6

The total yield of carboxylic acids, based on the amount of olefin charged, is 85% when 93–98% sulfuric acid is used. Below and above these concentrations, the yields hardly ever reach 50%. Using the acids formed from 1-hexene, 1-heptene, and 1-octene as examples, Table 5 shows that also amongst the tertiary acids isomers with the carboxyl group near the centre, are preferred as the length of the carbon chain of the olefin increases.

Table 5. Influence of the catalyst on the isomer ratios of tertiary carboxylic acids from the n-Δ^1-olefins hexene to decene. CO-pressure: 100 atm; temperature: +15 °C.

Olefin	-carboxylic acid	Isomers [%] Catalyst	
		contg. BF_3	H_2SO_4 (96 %)
1-Hexene	2-Methylpentane-2-	65.6	59.8
	3-Methylpentane-3-	34.4	40.2
1-Heptene	2-Methylhexane-2-	45.4	40.7
	3-Methylhexane-3-	54.6	59.3
1-Octene	2-Methylheptane-2-	39.0	28.8
	3-Methylheptane-3-	42.0	49.2
	4-Methylheptane-4-	18.8	22.0
1-Nonene	2-Methyloctane-2- / 3-Methyloctane-3-	65.3	54.8
	4-Methyloctane-4-	34.7	45.2
1-Decene	2-Methylnonane-2- / 3-Methylnonane-3-	53.6	50.5
	4-Methylnonane-4-	31.0	32.5
	5-Methylnonane-5-	15.4	17.0

Quantitative analysis of tertiary acids higher than C_{10} is very difficult, because 2-methylalkane-2-carboxylic esters cannot be separated from 3-methylalkane-3-carboxylic esters on moderatly polar columns and can be separated only incompletely on strongly polar columns. Details of the gas chromatographic separation of the methyl esters of secondary and tertiary acids will be reported elsewhere [12].

When the log of the retention volumes of the methyl esters are plotted against the number of carbon atoms, straight lines are obtained for homologous acids with equal branching, *e.g.* for the alkane-2-carboxylic acids, the alkane-3-carboxylic acids, the 2-methylalkane-2-carboxylic acids, and the 3-methylalkane-3-carboxylic acids. It is thus possible to identify those acids for which no specimens for comparison exist.

VI. Experimental

The experiments were carried out in a 1-litre autoclave made of V4A stainless steel containing 250 ml of catalyst. At a CO-pressure of 100 atm and a temperature of −5 °C or + 15 °C, 0.5 to 1.0 mole of olefin, diluted with 150 ml of n-hexane, were slowly injected. The total reaction took 2 to 5 hours and the solution was magnetically stirred throughout. The reaction product was decomposed with ice and the free carboxylic acids converted into their potassium salts and isolated. In the experiments in which alkoxofluoroboric acid served as catalyst, the organic phase was freed from acidic components by shaking with dilute sodium carbonate solution.

The free carboxylic acids were esterified with diazomethane or, using a slight modification of the method of *Metcalfe* et al. [13], by dissolving the acid in an excess of $BF_3 \cdot CH_3OH$. The reaction mixture was left standing overnight, decomposed with ice, and extracted with pentane after saturating the solution with $CaCl_2$. The pentane phase was dried and analyzed by gas chromatography.

I wish to thank Dr. G. Schomburg, for his help in carrying out and evaluating the numerous gas-chromatographic analyses and for his interest in discussing the results. I am specially indebted to Professor Dr. H. Koch who supported this work with his valuable help and advice

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[12] *G. Schomburg*, J. Chromatogr., in the press.

[13] *L. D. Metcalfe* and *A. A. Schmitz*, Analytic. Chem. 33, 363 (1961).

Phenol Oxidation Reactions

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Dedicated to Professor Dr. Hans Brockmann on the occasion of his 60th birthday

The use of well-known phenol oxidation reactions for the preparation of compounds arising from C–C and C–O coupling has recently received increased attention. A selection from the large number of products obtainable by oxidation of mono- and polyhydric phenols and a discussion of the reaction mechanisms indicate the scope of this method. The formation of hydroxyphenylquinones and orcein dyes from resorcinol derivatives is explained. The synthesis of natural products by way of phenol oxidations is briefly discussed.

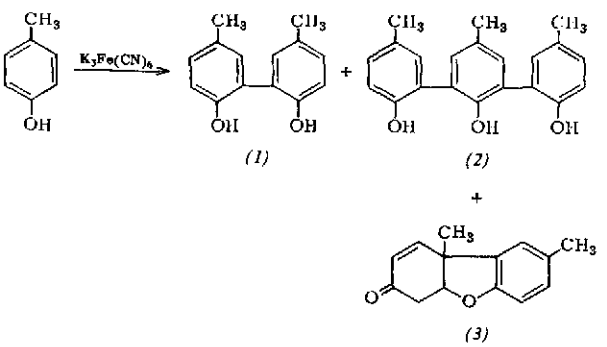
Introduction

Oxidation of phenols often produces a number of products that are sometimes polymeric and quinonoid in nature. Nevertheless, this reaction can be used to synthetize complicated compounds because, first of all, mixtures consisting of a number of similar components can now be separated nearly quantitatively by chromatography; furthermore several research groups have, for biogenetic reasons [1,2], renewed their efforts to synthetize natural products by oxidation of phenolic precursors and have developed procedures which sometimes afford the desired products in good yields. In the following, the principles and scope of oxidation of phenols, naphthols, and derivatives of hydroquinone, pyrocatechol, and resorcinol are discussed.

I. Oxidation of Monohydric Phenols and Naphthols

The variety of the oxidation products obtainable is clearly indicated by examples from the classical work of *H. Dianin*, of *R. Pummerer*, and of *H. Erdtman*, and by more recent work [3]. Generally, oxidation involves the removal of one hydrogen atom from each phenol molecule and leads exclusively to *o*- and *p*-linked dimeric and polymeric products, predominantly containing C–C, and more rarely, C–O linkages.

In aqueous alkaline solution, *p*-cresol reacts with potassium ferricyanide to produce, polymeric products plus the *o*-dimer *(1)*, the *o,o'*-trimer *(2)*, and Pummerer's ketone *(3)* [4–8]. The formation of *(3)* is explained on the basis of primary *o,p'*-coupling, followed by 1,2-addition of the *o'*-hydroxyl group onto the resulting cyclohexadienone [7].



The same products are formed on oxidation of *p*-cresol with ferric chloride [9], Fenton's reagent ($FeSO_4 + H_2O_2$) [10], or peroxidase plus H_2O_2 at pH 6.5 [11]; *Pseudomonas* enzymes preferably attack the methyl group instead [12].

α-Naphthol reacts with ferric chloride to produce all three possible *ortho*- and *para*-C–C-bonded products *(4)*, *(5)*, and *(6)* [13]. In acidic or neutral solution, β-naphthol affords 1,1'-binaphthol *(7)* in good yield; after oxidation with potassium ferricyanide in alkaline solution, on the other hand, only a small amount of the

[1] *D. H. R. Barton* and *T. Cohen* in: Festschrift für Arthur Stoll. Birkhäuser, Basel 1957, p. 117.

[2] *H. Erdtman* and *C. A. Wachtmeister* in: Festschrift für Arthur Stoll. Birkhäuser, Basel 1957, p. 144.

[3] The literature up to 1957 has been reviewed in [1] and [2] and by *B. S. Thyagarajan*, Chem. Reviews *58*, 439 (1958). See also *W. A. Waters*, Progr. org. Chem. *5*, 35 (1961); *J. D. Loudon*, ibid. *5*, 46 (1961).

[4] *R. Pummerer, H. Puttfarcken*, and *P. Schopflocher*, Ber. dtsch. chem. Ges. *58*, 1808 (1925).

[5] *C. G. Haynes, A. H. Turner*, and *W. A. Waters*, J. chem. Soc. (London) *1956*, 2823.

[6] *W. W. Kaeding*, J. org. Chemistry *28*, 1063 (1963).

[7] *D. H. R. Barton, A. M. Deflorin*, and *O. E. Edwards*, *J. chem.* Soc. (London) *1956*, 530.

[8] *V. Arkley, F. M. Deon, A. Robertson*, and *P. Sidisunthorn*, J. chem. Soc. (London) *1956*, 2322.

[9] *K. Bowden* and *C. H. Reece*, J. chem. Soc. (London) *1950*, 2249.

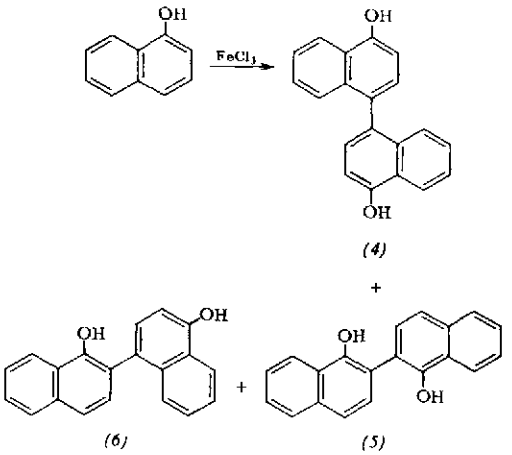
[10] *S. L. Cosgrove* and *W. A. Waters*, J. chem. Soc. (London) *1951*, 1726.

[11] *W. W. Westerfield* and *Ch. Lowe*, J. biol. Chemistry *145*, 463 (1942).

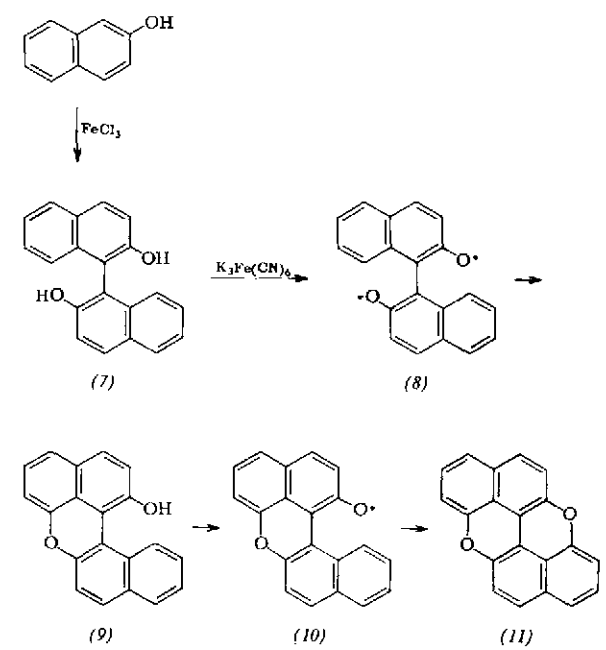
[12] *S. Dagley* and *M. D. Patel*, Biochem. J. *66*, 227 (1957).

[13] *J. D. Edwards* and *J. L. Cashaw*, J. Amer. chem. Soc. *76*, 6141 (1954).

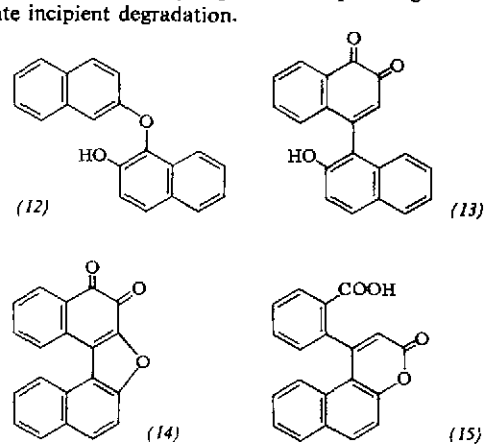
hydroxynaphthyl naphthyl ether *(12)* could be isolated [14,15]. The dimer *(7)* can be oxidized further with



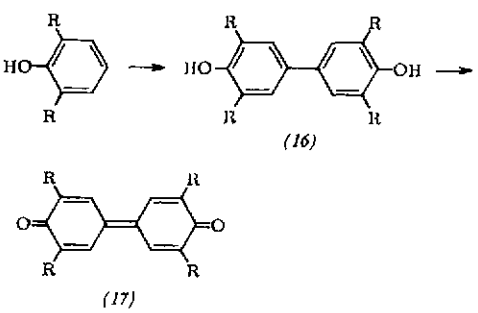
silver oxide [16] or potassium ferricyanide [17] to produce *(9)* and *(11)*. The formation of the purple radicals *(8)* and *(10)* that were postulated as early as 1914 has recently been verified by electron-spin resonance measurements [18].



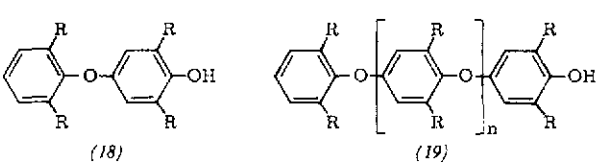
Treatment with hydrogen peroxide and ammonium molybdate gives a hydroxynaphthyl-*o*-naphthoquinone *(13)*, undoubtedly arising from oxidation of the β-naphthol to the *o*-quinone and subsequent addition of a second molecule of naphthol onto this quinone [19,20]. Treatment with solid sodium hydroxide and air at 70 °C affords 20 % of *(7)* and 20 % of *(14)*, in addition to *(15)* and other products [21], which, as in the oxidation of β-naphthol with permanganate [22], indicate incipient degradation.



If two of the three *o*- and *p*-positions are occupied by substituents, *o,o'*- and *p,p'*-bonded dimers of type *(16)* are produced in high yields. If the oxidizing agent has a sufficiently high oxidation potential, *p,p'*-bonding leads to the corresponding diphenoquinones *(17)*. Numerous examples of this reaction are known [3]. It is of interest, for the understanding of the biogenesis of diphenyl derivatives, that the common mushroom *Polyporus versicolor* contains an enzyme that catalyses this reaction [23].



Oxidation of 2-methoxyphenol (guaiacol) or 2,6-dimethylphenol with silver oxide in benzene affords dimers of types *(16)*, *(17)*, and *(18)* but also gives polymeric phenyl ethers *(19)* with molecular weights of up to 1900 [24] in yields as high as 40 %. If the oxidation is effected with air and cuprous chloride in nitrobenzene/pyridine, these yields decrease to zero, in favor of diphenoquinone formation, with increasing bulk of R [$-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$] [25].



[14] *R. Pummerer*, Ber. dtsch. chem. Ges. *52*, 1403 (1919).

[15] *R. Pummerer* and *E. Cherbuliez*, Ber. dtsch. chem. Ges. *52*, 1414 (1919).

[16] *R. Pummerer* and *F. Frankfurter*, Ber. dtsch. chem. Ges. *47*, 1472 (1914).

[17] *R. Pummerer* and *A. Rieche*, Ber. dtsch. chem. Ges. *59*, 2161 (1926).

[18] *A. Rieche, B. Elschner*, and *M. Landbeck*, Angew. Chem. *72*, 385 (1960).

[19] *I. D. Raacke-Fels, C. H. Wang, R. K. Robins*, and *B. E. Christensen*, J. org. Chemistry *15*, 627 (1950).

[20] *A. Bader*, J. Amer. chem. Soc. *73*, 3731 (1951).

[21] *G. Brunnstrom*, J. Amer. chem. Soc. *77*, 2463 (1955).

[22] *O. Dischendorfer* and *W. Danziger*, Mh. Chem. *48*, 315 (1927).

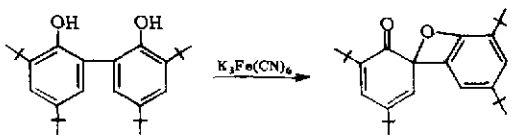
[23] *S. M. Bocks, B. R. Brown*, and *A. H. Todd*, Proc. chem. Soc. (London) *1962*, 117.

[24] *B. O. Lindgren*, Acta chem. scand. *14*, 1203, 2089 (1960).

[25] *A. S. Hay, H. S. Blanchard, G. F. Endres*, and *J. W. Eustance*, J. Amer. chem. Soc. *81*, 6335 (1959).

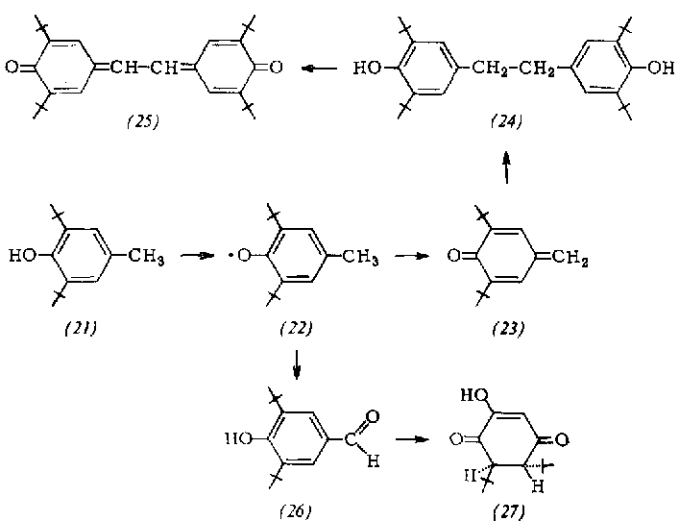
It is noteworthy that, in this case, partial exchange of the *meta*-hydrogen takes place despite the fact that coupling occurs only in the *para*-position [26] and, moreover, that oxidation with oxygen and laccase or peroxidase leads only to C–C coupling, with no formation of ethers [24]. Oxidation of *p*-halogenophenols with potassium ferrycianide or lead dioxide proceeds by way of a radical chain reaction and also affords polymeric phenyl ethers (molecular weight = 2000–10000) [27].

The formation of quinol ethers is preferentially intramolecular when the phenol residues to be coupled are already linked by a C–C bridge, *e.g. (20)* [28]; cf. also [29,30]. Intermolecular ether formation is favored only when C–C coupling is sterically hindered [143].



(20)

Linking through methyl groups is particularly noticeable in the oxidation of 2,6-di-t-butyl-4-methylphenol *(21)*. Oxidation with lead dioxide and silver oxide or potassium ferricyanide leads by way of the radical *(22)* to the very unstable quinone methide *(23)* which then dimerizes to give *(24)* and *(25)* [31,32].



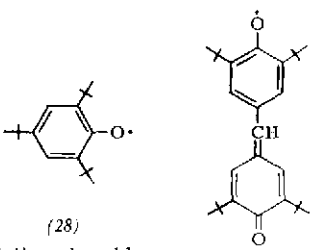
(25) *(24)* *(21)* *(22)* *(23)* *(26)* *(27)*

Treatment with atmospheric oxygen in alkaline solution affords the aldehyde *(26)* besides *(24)* and *(25)* [33]. More vigorous conditions lead to degradation of the aldehyde by a mechanism which has not yet been explained but which probably proceeds via a carboxylic acid intermediate and yields *(27)* [34].

If the methylene groups are protected by substituents such as methyl or phenyl residues, the quinone methides *(23)* can sometimes be isolated [32,35].

II. Stable Phenoxy Radicals

The presence of large substituents, *e.g.* t-butyl groups or phenyl residues, at all the *o*- and *p*-positions stabilizes the primary oxidation products, *i.e.* free phenoxy radicals. Some of these free radicals form dark-colored crystals, *e.g. (28)* [36] and *(28a)* [38]; cf. [35–40]; others undergo association in the crystals to form colorless dimeric quinol ethers, which in solution dissociate to varying degrees into radicals, *e.g. (29)* [46,47]; cf. [41–45].

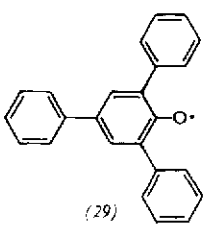


(28)

solution: deep blue
crystal: deep blue

(28a)

solution: λ_{max} = 423 mμ
crystal: deep blue



(29)

solution: red
crystal: colorless, dimer

[26] *W. A. Butte* and *C. C. Price*, J. Amer. chem. Soc. *84*, 3567 (1962).

[27] *G. D. Staffin* and *C. C. Price*, J. Amer. chem. Soc. *82*, 3633 (1960); *J. Bourdon* and *M. Calvin*, J. org. Chemistry *22*, 101 (1957); *M. Hedayatullah* and *U. L. Denivelle*, C. R. hebd. Séances Acad. Sci. *254*, 2369 (1962); *E. Müller, A. Rieker*, and *W. Beckert*, Z. Naturforsch. *17b*, 567 (1962).

[28] *E. Müller, R. Mayer, B. Narr, A. Rieker*, and *K. Scheffler*, Liebigs Ann. Chem. *645*, 25 (1961).

[29] *R. Pummerer* and *E. Cherbuliez*, Ber. dtsch. chem. Ges. *47*, 2957 (1914); *J. N. Chatterjea*, J. Indian chem. Soc. *35*, 37 (1958); Ref. C *1960*, 1499.

[30] *D. R. Nelan* and *C. D. Robeson*, J. Amer. chem. Soc. *84*, 2963 (1962); *P. Schudel, H. Mayer, J. Metzger, R. Rüegg*, and *O. Isler*, Helv. chim. Acta *46*, 636 (1963); *D. McHall* and *I. Green*, Chem. and Ind. *1963*, 982.

[31] *S. L. Cosgrove* and *W. A. Waters*, J. chem. Soc. (London) *1951*, 388; *G. R. Yohe, D. R. Hill, J. E. Dunbar*, and *F. M. Scheidt*, J. Amer. chem. Soc. *75*, 2688 (1953); *C. D. Cook, N. G. Nahs* and, *H. R. Flanagan*, ibid. *77*, 1783 (1955); *75*, 6242 (1953).

[32] *C. D. Cook* and *B. Norcross*, J. Amer. chem. Soc. *78*, 3797 (1956); *L. J. Filar* and *S. Winstein*, Tetrahedron Letters *1960*, 25 9; *A. Hubele, H. Suhr*, and *U. Heilmann*, Chem. Ber. *95*, 639 (1962); *R. H. Bauer* and *G. M. Coppinger*, Tetrahedron *19*, 1201 (1963).

[33] *G. R. Yohe, J. E. Dunbar, R. L. Pedrotti, F. M. Scheidt, F. G. H. Lee*, and *E. C. Smith*, J. org. Chemistry *21*, 1289 (1956).

[34] *G. R. Yohe, J. E. Dunbar, M. W. Lansford, R. L. Pedrotti, F. M. Scheidt, F. G. Lee*, and *E. C. Smith*, J. org. Chemistry *24*, 1251 (1959); see also *J. K. Becconsall, S. Clough*, and *F. Scott*, Trans. Faraday Soc. *56*, 459 (1960).

[35] *C. D. Cook* and *N. D. Gilmour*, J. org. Chemistry *25*, 1429 (1960).

[36] *E. Müller* and *K. Ley*, Chem. Ber. *87*, 922 (1954); *C. D. Cook* and *R. C. Woodworth*, J. Amer. chem. Soc. *75*, 6242 (1953); *C. D. Cook*, J. org. Chemistry *18*, 261 (1953).

[37] *E. Müller, R. Mayer*, and *K. Ley*, Angew. Chem. *70*, 73 (1958).

[38] *G. M. Coppinger*, J. Amer. chem. Soc. *79*, 501 (1957); *P. D. Bartlett* and *T. Funahashi*, ibid. *84*, 2596 (1962); *M. S. Kharasch* and *B. S. Yoshi*, J. org. Chemistry *22*, 1435 (1957).

[39] *K. Ley, E. Müller*, and *K. Scheffler*, Angew. Chem. *70*, 74 (1958).

[40] *E. Müller, A. Schick*, and *K. Scheffler*, Chem. Ber. *92*, 474 (1959); *W. R. Hatchard, R. D. Lipscomb*, and *F. W. Stacey*, J. Amer. chem. Soc. *80*, 3636 (1958).

[41] *E. Müller* and *K. Ley*, Chem. Ber. *88*, 601 (1955).

[42] *K. Ley, K. Scheffler, A. Rieker*, and *E. Müller*, Z. Naturforsch. *13b*, 460 (1956); *E. Müller, A. Rieker, K. Ley, R. Mayer*, and *K. Scheffler*, Chem. Ber. *92*, 2278 (1959).

[43] *K. Ley, E. Müller*, and *G. Schlechte*, Chem. Ber. *90*, 1530 (1957).

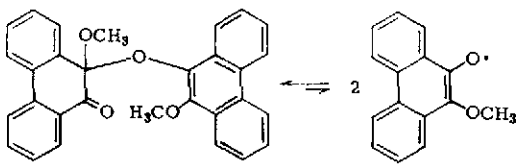
[44] *E. Müller, K. Ley*, and *W. Schmidhuber*, Chem. Ber. *89*, 1738 (1956); *C. D. Cook, P. A. Kuhn*, and *P. Fianu*, J. Amer. chem. Soc. *78*, 2002 (1956).

[45] *E. Müller, A. Schick, R. Mayer*, and *K. Scheffler*, Chem. Ber. *93*, 2649 (1960).

[46] *K. Dimroth, F. Kalk*, and *G. Neubauer*, Chem. Ber. *90*, 2058 (1957); *K. Dimroth, F. Kalk, R. Sell*, and *K. Schlömer*, Liebigs Ann. Chem. *624*, 51 (1959); *K. Dimroth*, Angew. Chem. *72*, 714 (1960).

[47] *E. Müller, K. Ley*, and *G. Schlechte*, Chem. Ber. *90*, 2660 (1957).

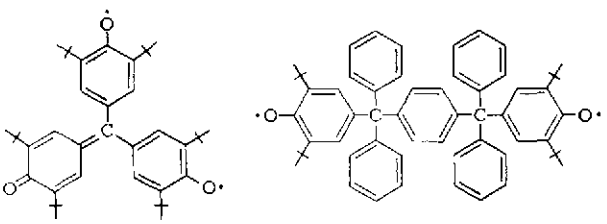
The compound known as Goldschmidt's oxygen radical [48] also exists in the crystal in the form of the dimeric colorless quinol ether *(30)* and was shown by electron spin resonance measurements to dissociate on dissolution into the yellow-green radical *(31)* only to the extent of 0.1% [49].



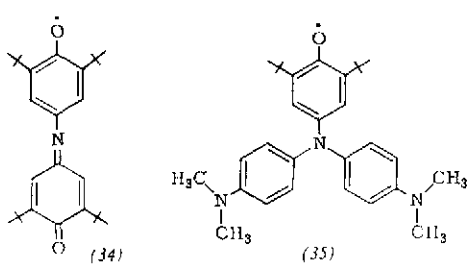
(30) *(31)*

The reactivity of these radicals towards oxygen decreases with increasing phenyl substitution. The 2,4,6-triphenylphenoxy radical *(29)* is surprisingly stable towards oxygen [45–47].

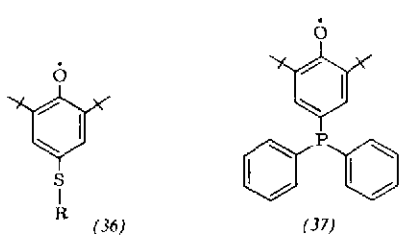
Diradicals such as *(32)* [50] and *(33)* [51] and nitrogenous radicals such as *(34)* [52] and *(35)* [53] – which are very stable to oxygen – can be prepared. The existence, in solution, of the unstable, red radicals containing sulfur and phosphorus *(36)* [54] and *(37)* [55] has been demonstrated.



(32) *(33)*



(34) *(35)*



(36) *(37)*

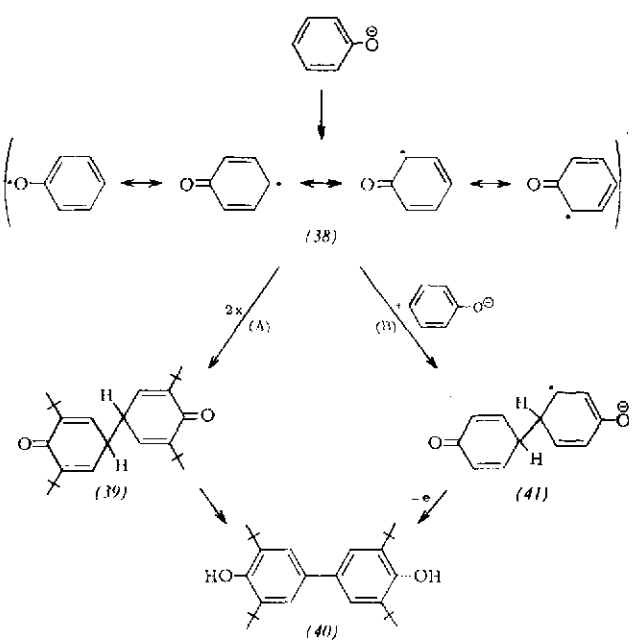
These radicals were detected by their magnetic susceptibility and electron-spin resonance. They all are characteristically colored and show an absorption band in the infrared near 1560 cm^{-1}; they differ markedly from the colorless, dimeric quinol ethers which have a doublet at 1660 and 1640 cm^{-1} in the infrared spectrum [45,47]. Because of resonance stabilization, unsubstituted phenoxyl radicals *(38)* have a longer life-time than alkyl or aryl radicals and do not tend to attack the solvent or to initiate olefin polymerization as readily.

Analysis of the hyperfine splitting of the ESR spectra shows that the probability for the occurrence of the free electron at the *para*-carbon atom is greater than that at the *ortho*-position and, surprisingly, that it is lower at the *meta*-position, but not zero; furthermore, the analysis shows that the free electron can also distribute itself over alkyl groups and hetero-atoms in the *ortho*- and *para*-positions [54–57]. With a phenyl residue in the *p*-position, the radical electron is distributed more readily than when this residue is in the *o*-position where the oxygen forces it out of the molecular plane to a greater extent [40,45].

Whether and to what extent the density of the radical electron on the oxygen is reduced or increased by substituents capable of resonance is not yet known. It is to be expected that the hyperfine structure of ESR spectra of ^{13}C-labelled phenoxyl radicals will provide an answer to this interesting question [58].

III. Oxidizing Agents and Coupling Mechanisms

In all the cases cited, silver oxide, lead dioxide, and manganese dioxide in slightly polar solvents, electrochemical oxidation [59], or potassium ferricyanide in alkaline solution afford phenoxyl radicals *(38)* in the first reaction step, which usually undergo further reactions very rapidly.



(38) *(39)* *(40)* *(41)*

[48] *St. Goldschmidt*, Ber. dtsch. chem. Ges. *55*, 3194 (1922); *St. Goldschmidt* and *W. Schmidt*, Ber. dtsch. chem. Ges. *55*, 3197 (1922).

[49] *E. Müller, K. Schurr*, and *K. Scheffler*, Liebigs Ann. Chem. *627*, 132 (1959).

[50] *N. C. Yang* and *A. J. Castro*, J. Amer. chem. Soc. *82*, 6208 (1960).

[51] *E. Müller, R. Mayer*, and *K. Scheffler*, Z. Naturforsch. *13b*, 825 (1958).

[52] *G. M. Coppinger*, Tetrahedron *18*, 61 (1962).

[53] *O. Neunhoeffer* and *P. Heitmann*, Chem. Ber. *96*, 1027 (1963).

[54] *E. Müller, H. B. Stegmann*, and *K. Scheffler*, Liebigs Ann. Chem. *645*, 79 (1961).

[55] *E. Müller, H. Eggensperger*, and *K. Scheffler*, Liebigs Ann. Chem. *658*, 103 (1962).

[56] *E. Müller, K. Ley, K. Scheffler*, and *R. Mayer*, Chem. Ber. *91*, 2682 (1958); *E. Müller, R. Mayer, H.-D. Spanagel*, and *K. Scheffler*, Liebigs Ann. Chem. *645*, 53 (1961); *E. Müller, R. Mayer, U. Heilmann*, and *K. Scheffler*, ibid. *645*, 66 (1961); *E. Müller, A. Rieker*, and *K. Scheffler*, ibid. *645*, 92 (1961).

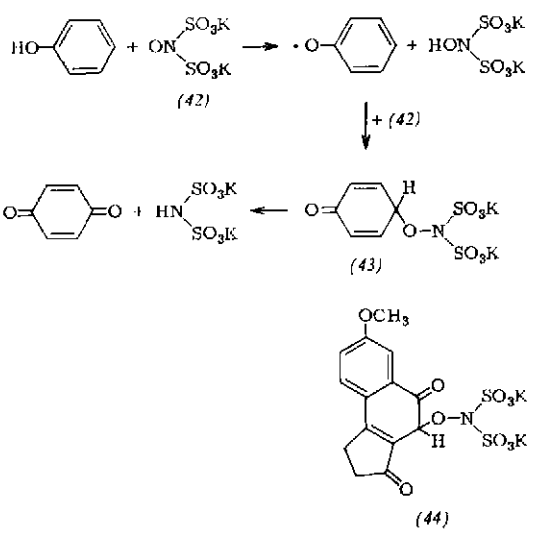
[57] *K. Schäfer*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *65*, 439 (1961).

[58] Investigations of this kind are in progress: *E. Müller*, personal communication.

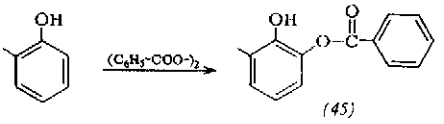
[59] *F. Fichter* and *F. Ackermann*, Helv. chim. Acta *2*, 583 (1919).

Generally, C–C or C–O coupling can occur in one of two ways. Two radicals can dimerize (A) to give the cyclohexadienone *(39)* which, in the case of the 2,6-t-butyl compound, can be isolated and which rearranges in methanol, to the dimeric phenol *(40)* [60]. Alternatively, when the oxidation is slow, dimerization is not likely to occur because of the low radical concentration. Under these conditions, in particular, it is possible that the phenoxide ions or phenol molecules, which are present in high concentrations, undergo electrophilic substitution by the radical (B), the radical *(41)* being dehydrogenated further to give the dienone or diphenol. Support for the latter alternative has not yet been obtained. It should be noted in this connection that oxidation of a mixture of 2,6-dimethylphenol and 2,6-dimethoxyphenol with potassium ferricyanide gives only symmetric and no asymmetric diphenoquinones [5].

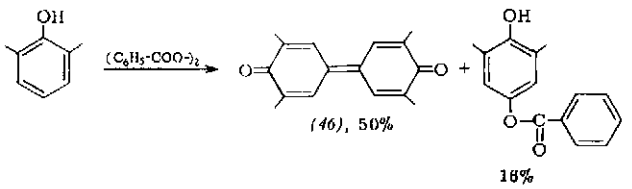
Oxidizing agents which readily liberate oxygen, *e.g.* hydrogen peroxide or OH radicals (Fenton's reagent), organic peroxides, periodic acid, persulfate, lead tetraacetate, or potassium nitrosodisulfonate *(42)* [Fremy's salt], often produce monomeric *p*- and *o*-quinones and their reaction products or quinol derivatives in addition to polymers. The preparative synthesis of quinones is readily accomplished by the Elbs persulfate oxidation [61] and, in particular, by oxidation with Fremy's salt according to *Teuber* [62]. In the latter case, two moles of Fremy's salt are consumed and produce one mole each of imidodisulfonic acid and hydroxylamine-*N*,*N*-disulfonic acid. The first mole of *(42)* produces the free phenoxyl radical which then reacts with the second mole to give the quinol *(43)*. The formation of such quinols can be demonstrated in the case of certain naphthol derivatives, *e.g.* *(44)*; they decompose into the quinone and imidodisulfonic acid [63]. This process yields preferentially *p*-quinones. If the *para*-position is occupied by alkyl groups, *o*-quinones can be isolated.



Labile *o*-quinones [64] and hydroxyquinones [65, 66] can be prepared in this manner in good to very good yields, provided that the redox potential of the quinone to be formed is not too high.

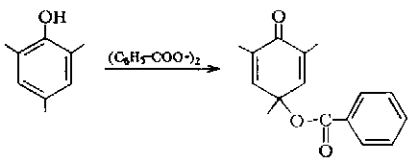


(45)



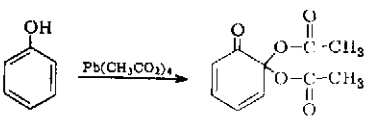
(46), 50%

16%

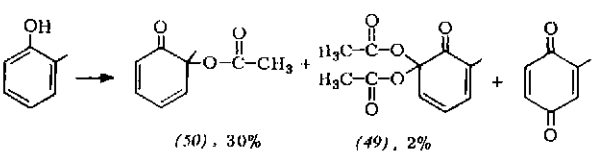


(47), 90%

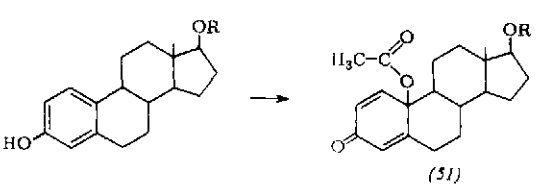
Oxidation with hydroxyl radicals affords dimeric or hydroxylated products [10,67]. Thus, 2,6-di-t-butyl-4-methylphenol reacts with t-butyl hydroperoxide to give the t-butylperoxo-*p*-quinol [68]. Benzoyl peroxide yields 6-benzoyloxypyrocatechol *(45)*, diphenoquinones *(46)*, or the *O*-benzoyl derivatives of *p*-quinols *(47)* [69].



(48)



(50), 30% *(49)*, 2%



(51)

depending on the substituents. Oxidation with lead tetraacetate leads to 2,2-diacetoxycyclohexadienones ("quinone diacetates") *(48)* and *(49)*, *O*-acetylquinols

[60] *M. S. Kharasch* and *B. S. Yoshi*, J. org. Chemistry *22*, 1439 (1957); *K. Ley*, *E. Müller*, *R. Mayer*, and *K. Scheffler*, Chem. Ber. *91*, 2670 (1958).

[61] *W. Baker* and *N. C. Brown*, J. chem. Soc. (London) *1948*, 2303; Review: *J. D. Loudon*, Progr. org. Chem. *5*, 56 (1961).

[62] *H. J. Teuber* and *W. Rau*, Chem. Ber. *86*, 1036 (1953); *H. J. Teuber* and *N. Götz*, ibid. *87*, 1236 (1954).

[63] *H. J. Teuber* and *N. Götz*, Chem. Ber. *89*, 2654 (1956); *H. J. Teuber* and *G. Thaler*, ibid. *92*, 667 (1959).

[64] *H. J. Teuber* and *G. Staiger*, Chem. Ber. *88*, 802 (1955).

[65] *H. Musso*, Chem. Ber. *91*, 349 (1958).

[66] *H. Musso* and *H. Beecken*, Chem. Ber. *92*, 1416 (1959); *H. Musso* and *H.-G. Matthies*, ibid. *94*, 356 (1961).

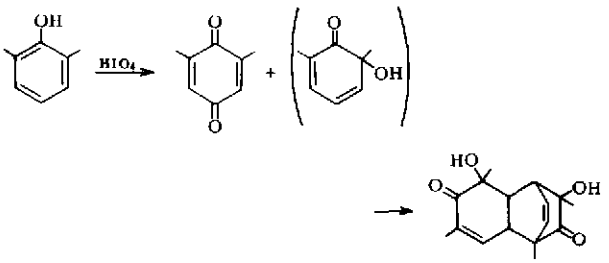
[67] *D. G. H. Daniels* and *B. C. Saunders*, J. chem. Soc. (London) *1951*, 2112, 3433.

[68] *T. W. Campbell* and *G. M. Coppinger*, J. Amer. chem. Soc. *74*, 1469 (1952).

[69] *C. Walling* and *R. B. Hodgdon*, J. Amer. chem. Soc. *80*, 228 (1958); *S. L. Cosgrove* and *W. A. Waters*, J. chem. Soc. (London) *1949*, 3189; *1951*, 388.

("quinol acetates"), *(50)* and *(51)* [67], and quinones [70–72].

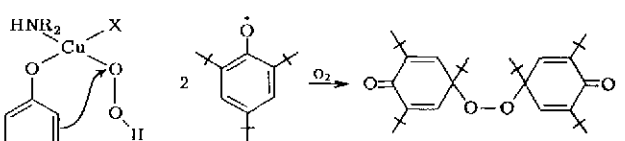
The reaction mechanism has not been definitely elucidated, because the solution gives an ESR signal only after the quinol formation is complete [72]. Periodic acid affords oxidation products that are similar to those obtained with lead tetraacetate; the free quinols dimerize readily, *e.g.* to *(52)*; hydroquinone monoethers are readily cleaved [73].



(52)

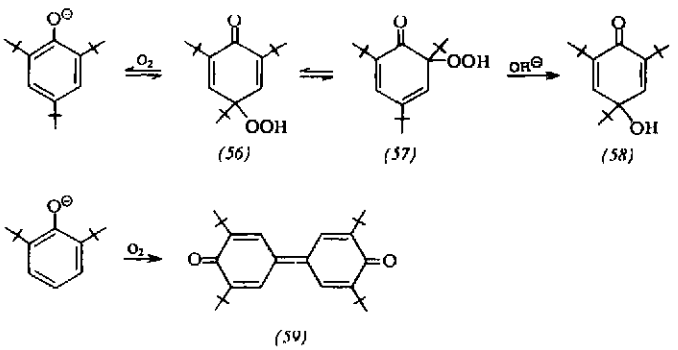
Oxidations with persulfate and silver ions [74], perchloryl fluoride [75], or trifluoroperoxyacetic acid [76] offer no preparative advantages.

Hydroxylation of phenols in the *o*-position can be accomplished with oxygen and copper(II) ions, in the presence of a secondary amine such as morpholine [77]. However, the resulting pyrocatechols are oxidized further to *o*-quinones which rapidly add onto the base. The exclusive attack at the *ortho*-position can be explained by assuming the formation of a copper complex *(53)*. Analogous products are obtained enzymatically using tyrosinase [78]; the formation of a complex with copper can be considered as a model for the mode of activity of the latter.



(53) *(54)* *(55)*

Sterically hindered free phenoxyl radicals, *e.g.* the dark-blue tri-t-butylphenoxyl radical *(54)*, react rapidly with oxygen to produce quinol peroxides, *e.g.* *(55)* [36]. Direct oxidation of phenoxide ions with oxygen affords 2- and 4-hydroperoxycyclohexadienones *(56)* and *(57)*, which in alkaline solution undergo decomposition to quinols *(58)*. If the *p*-position is free, no oxygen is absorbed; instead, diphenoquinone *(59)* is



(56) *(57)* *(58)* *(59)*

produced. This shows that a sterically unhindered phenoxyl radical reacts faster with itself than with oxygen [60,79,80].

Each of the pure hydroperoxycyclohexadienones *(56)* and *(57)* undergoes isomerization in the presence of alkali and oxygen to the equilibrium mixture of *(56)* and *(57)*. If nitrogen is bubbled through the solution the oxygen is removed and 70% of the original phenol can be recovered. The reaction is of the first order with respect to phenol and oxygen and is catalysed by both 2,6-di-t-butylbenzoquinone and *m*-dinitrobenzene [81]. Its reversibility can be explained by the greater resonance stabilization of the phenoxide ion compared to the cyclohexadienonyl hydroperoxide anion; it is represented by the following equilibria [81] (C = catalyst):

$$C + R^{\ominus} + O_2 \leftrightharpoons C^{\ominus}_{\bullet} + R\bullet + O_2 \leftrightharpoons C^{\ominus}_{\bullet} + R{-}O{-}O\bullet \leftrightharpoons C + R{-}O{-}O^{\ominus}$$

IV. Redox Potential and Rate of Oxidation

The potential of reversible redox systems can be readily determined by a redox titration. This is not possible for irreversible oxidations. With the exception of the stable phenoxyls, most of the radicals cited herein react further at a rate which is too fast for determining their potential by titration of the phenol with the oxidizing agent. The semi-quantitative method of *Fieser* [82] is useful in this respect. It consists of testing the phenol with different oxidizing agents of known redox potential to determine which one is just insufficient to oxizide the phenol under standard conditions. These "critical potentials" are not accurate; however, they do provide useful orientation in the "electrochemical series" of phenols [5,83]. Since a linear relationship exists between the empirically determined critical potentials and the theoretical energy values for the highest occupied phenol orbitals as calculated by the LCAO-MO method, it can

[70] *W. Metlesics, E. Schinzel, H. Vilesek*, and *F. Wessely*, Mh. Chem. *88*, 1069 (1957); *G. Billek, J. Swoboda*, and *F. Wessely*, Tetrahedron *18*, 909 (1962) and previous publications.

[71] *E. Hecker*, Chem. Ber. *92*, 1386, 3198 (1959).

[72] *E. Hecker* and *R. Lattrell*, Liebigs Ann. Chem. *662*, 48 (1963).

[73] *E. Adler, J. Dahlén*, and *G. Westin*, Acta chem. scand. *14*, 1580 (1960); *E. Adler, I. Falkehag*, and *B. Smith*, ibid. *16*, 529 (1962) and previous publications.

[74] *R. G. R. Bacon* and *D. J. Munro*, J. chem. Soc. (London) *1960*, 1339.

[75] *A. S. Kende* and *P. McGregor*, J. Amer. chem. Soc. *83*, 4197 (1961).

[76] *J. D. McClure*, J. org. Chemistry *28*, 69 (1963).

[77] *W. Brackman* and *E. Havinga*, Recueil Trav. chim. Pays-Bas *74*, 937, 1021, 1070, 1100, 1107 (1955); *E. Talman*, Ph. D. Thesis, Universität Leiden (Holland) 1961.

[78] *C. E. M. Pugh* and *H. S. Raper*, Biochem. J. *21*, 1370 (1927); *J. Neumann, G. Legrand, G. Lehongre*, and *J. Lavollay*, C. R. hebd. Séances Acad. Sci. *252*, 309 (1963).

[79] *K. Ley*, Angew. Chem. *70*, 74 (1958).

[80] *H. S. Blanchard*, J. org. Chemistry *25*, 264 (1960).

[81] *H. R. Gersmann* and *A. F. Bickel*, J. chem. Soc. (London) *1959*, 2711; *1962*, 2356.

[82] *L. F. Fieser*, J. Amer. chem. Soc. *52*, 4915, 5204 (1930).

[83] *N. S. Hush*, J. chem. Soc. (London) *1953*, 2375.

be assumed that the rate-determining step, in all cases, involves removal of one electron from the highest occupied orbital [84]. The higher the redox potential of the oxidizing agent [96] compared to that of the phenol, the faster the oxidation should be (cf. [84a]).

On the other hand, polarographic analysis of many irreversibly oxidizable phenols shows waves [85, 86] which correspond to "relative oxidation potentials". Since the half-wave potential obtained for reversible systems, *e.g.* quinones/hydroquinones, are comparable, at least in their sequence, with the actual redox potentials [87], it should also be possible to use the relative oxidation potentials of irreversible phenol oxidations as a measure of phenol oxidizability (Fig. 1).

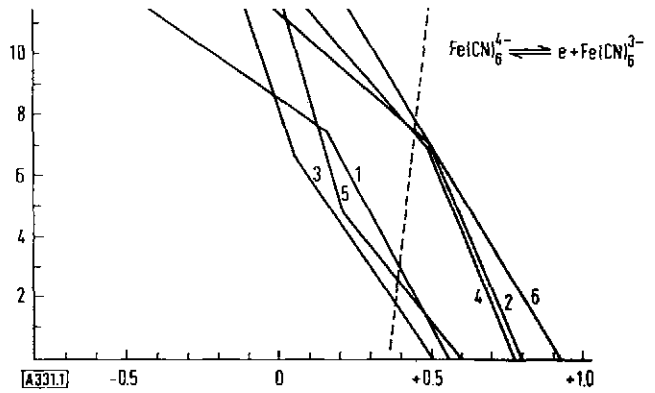


Fig. 1. Dependence on pH of the relative oxidation potentials of some phenols [85, 86].

1. Hydroquinone
2. Resorcinol
3. Pyrogallol
4. Phoroglucinol
5. Pyrocatechol
6. Phenol

Ordinate: pH

Abscissa: Relative oxidation potential [v].

Qualitative and quantitative data for the rate of oxidation of several phenols with the diphenylpicrylhydrazyl radical [97] and periodic acid [88] show that monohydric phenols and resorcinol react much slower than hydroquinone and pyrocatechol [89] and that the reaction rate of phenol increases with increasing alkyl substitution [90]. The same is true for the oxidation with atmospheric oxygen in aqueous alcoholic alkali hydroxide (Fig. 2) [91]. On autoxidation of alkyl-substituted hydroquinones in aqueous alcoholic buffer solutions with equal phenoxide concentrations, a linear relationship is

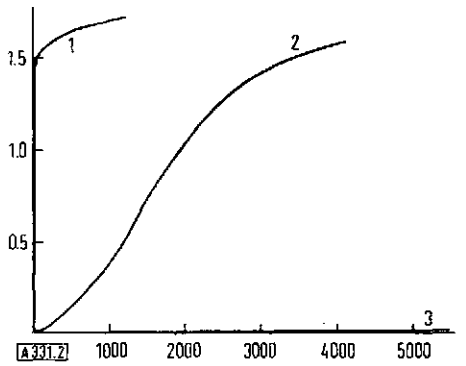


Fig. 2. Rate of autoxidation of phenols in methanol/water (1:1) at pH 13.

Curve 1: Hydroquinone and pyrocatechol
Curve 2: Resorcinol
Curve 3: 2,3,5-Trimethylphenol

The curve for hydroxyhydroquinone coincides with the ordinate. The curve for phenol coincides with the abscissa.

Ordinate: Oxygen absorbed [moles of O_2]
Abscissa: Time [min]

obtained between the redox potentials and the logarithms of the time for absorption of one half of the oxygen [91] (Fig. 3).

The redox potential and stability of a phenoxyl radical determine its effectiveness as an autoxidation inhibitor [85, 86, 92]. 2,6-Di-t-butyl-4-methylphenol is particularly well suited for this purpose [93].

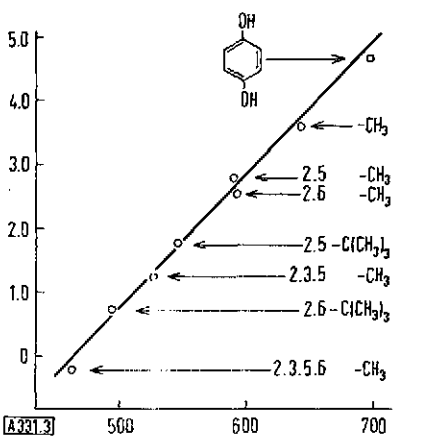


Fig. 3. Dependence of the half-life period for the autoxidation of alkyl-substituted hydroquinones on the redox potential at pH = (pK_2 − 3.8).

Ordinate: log $t_{1/2}$ [$t_{1/2}$ in min]
Abscissa: Redox potential E_0 [mv]

As indicated by Figure 1, the oxidation of, for example, pyrocatechol with potassium ferricyanide in alkaline solution is definitely possible. Oxidation occurs even if the potential of the oxidizing agent is 0.1 volt lower than that of the phenol, provided that the resulting phenoxyl is rapidly removed from the equilibrium (*e.g.* by dimerization).

It should be mentioned that attempts have been made [94] to determine the position of the equilibrium between various

[84] *T. Fueno, T. Lee*, and *H. Eyring*, J. physik. Chem. *63*, 1940 (1959).

[84a] *O. Dimroth*, Angew. Chem. *46*, 571 (1933).

[85] *G. E. Penketh*. J. appl. Chem. *7*, 512 (1957).

[86] We thank Dr. *H. Berg*, Jena, for polarographic determinations of further compounds. For the polarography of stable phenoxy radicals see *F. W. Steuber*, Ph. D. Thesis, Universität Marburg, 1963.

[87] *H. Musso, K. Figge*, and *D. Becker*, Chem. Ber. *94*, 1107 (1961).

[88] *J. P. Feiser, M. A. Smith*, and *B. R. Willeford*, J. org. Chemistry *24*, 90 (1959).

[89] *P. Venker* and *H. Herzmann*, Naturwissenschaften *47*, 133 (1960).

[90] *J. C. McGowan* and *T. Powell*, J. chem. Soc. (London) *1961*, 2160.

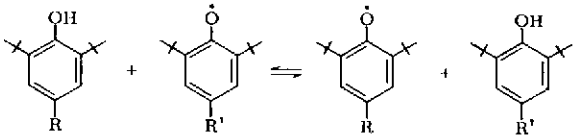
[91] *H. Musso* and *H. Franke*, unpublished results.

[92] *J. L. Bolland* and *P. ten Have*, Discuss. Faraday Soc. *2*, 252 (1947); vgl. auch *K. U. Ingold* and *J. A. Howard*, Nature (London) *195*, 280 (1962).

[93] *W. A. Waters*, Progr. org. Chem. *5*, 21 (1961).

[94] *C. D. Cook, C. B. Depatie*, and *E. S. English*, J. org. Chemistry *24*, 1356 (1959); see also [85] and *K. I. Krafft*, Ph. D. Thesis, Universität Marburg, 1963.

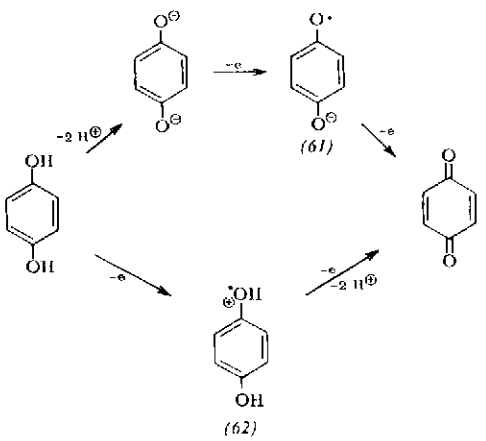
stable phenoxyl radicals, *e.g. (60a)* and *(60b)*, and hence to evaluate their redox potentials, and that the rate constant for hydrogen transfer for R = R' = t-butyl has been determined by measurement of the broadening of NMR signals in carbon tetrachloride and found to be $k = 300$ mole$^{-1}\times$ sec^{-1}. The temperature-dependence of this constant indicated an activation energy of only 1 kcal/mole [95].



(60a) *(60b)*

V. Oxidation of Derivatives of Hydroquinone, Pyrocatechol, and Pyrogallol

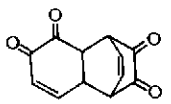
Oxidation of derivatives of hydroquinone and pyrocatechol with all oxidizing agents first yields *p*- or *o*-quinones. Depending on the reaction conditions, these can be isolated or they rapidly react further with nucleophilic reactants. Humic acid-type polymers are usually the final products. Here, too, the first step involves a one-electron transfer with formation of the semiquinone which has such a long life-time – in strongly alkaline solution in the form of the symmetric resonance-stabilized anion *(61)* and in strongly acidic solution as the cation *(62)* – that it can be identified by titration [98], spectroscopically [99,100], or by ESR measurements [101].



(61) *(62)*

The equilibrium quinone + hydroquinone $\rightleftharpoons$ semiquinone radical anion *(61)* is established very rapidly, with $k_1 = 2.6\times 10^8$ mole$^{-1}\cdot$sec^{-1}, whereas the subsequent reaction affording hydroxyhydroquinone is substantially slower, with $k = 2.3$ [99]. In the case of 2,4-di-t-butylpyrocatechol, the Li, Na, and K salts of the semiquinone radical anion have been isolated in the form of their crystalline etherates [102].

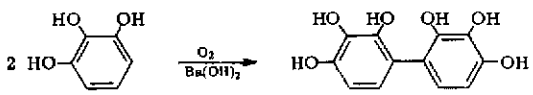
A method that is very suitable for the preparative synthesis of labile *o*-quinones from pyrocatechol, in addition to Willstätter's silver oxide method and the Teuber oxidation, is the oxidation with tetrachloro-*o*-quinone (*o*-chloranil) [103] because, in this case, no water is formed.



(63)

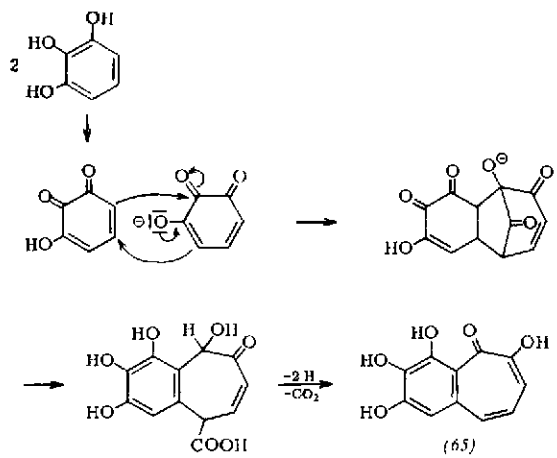
The structures of the dimeric *o*-quinones were identified as the diene adducts *(63)* [104]. For the mechanism of oxidation of pyrocatechol to *cis,cis*-muconic acid, see [105]. *o*-Diphenoquinones can also be prepared [106].

Pyrogallol [107] or gallic acid esters [108] can undergo biphenyl coupling, for example to produce *(64)*. The reaction probably involves the addition of a pyrogallol anion onto a molecule of hydroxy-*o*-quinone.



(64)

The formation of purpurogallin *(65)* from pyrogallol by the action of potassium iodate was explained by Scheme 1 [109,110]:



(65)

Scheme 1. Formation of purpurogallin from pyrogallol.

[95] *R. W. Kreilick* and *S. I. Weissmann*, J. Amer. chem. Soc. *84*, 306 (1962).

[96] Redox potentials of oxidizing agents are reviewed by *F. Seel*: Grundlagen der analytischen Chemie in wäßrigen Systemen. Verlag Chemie, Weinheim/Bergstr. 1955.

[97] According to *E. A. Braude, A. G. Brook*, and *R. P. Linstead*, J. chem. Soc. (London) *1954*, 3574, the redox potential of diphenylpikrylhydrazyl is 1.20 v at pH 0.

[98] *L. Michaelis, M. P. Schubert*, and *S. Granick*, J. Amer. chem. Soc. *61*, 1981 (1939).

[99] *H. Diebler, M. Eigen*, and *P. Matthies*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *65*, 634 (1961); *M. Eigen* and *P. Matthies*, Chem. Ber. *94*, 3309 (1960).

[100] *W. Flaig* and *J. Ch. Salfeld*, Naturwissenschaften *47*, 516 (1960).

[101] Review: *A. Carrington*, Quart. Rev. *17*, 67 (1963).

[102] *K. Ley* and *E. Müller*, Angew. Chem. *70*, 469 (1958).

[103] *L. Horner* and *W. Dürkheimer*, Z. Naturforsch. *14b*, 741 (1959).

[104] *L. Horner* and *K. Sturm*, Liebigs Ann. Chem. *597*, 1 (1955); *B. Witkop*, J. org. Chemistry *22*, 1477 (1957); *J. Harley-Mason* and *A. H. Laird*, J. chem. Soc. (London) *1958*, 1718.

[105] *A. A. Patchett* and *B. Witkop*, J. org. Chemistry *22*, 1477 (1957); *O. Hayaishi, A. A. Patchett*, and *B. Witkop*, Liebigs Ann. Chem. *608*, 158 (1957).

[106] *D. Schulte-Frohlinde* and *F. Erhardt*, Angew. Chem. *74*, 116 (1962); Angew. Chem. internat. Edit. *1*, 112 (1962).

[107] *C. Harries*, Ber. dtsch. chem. Ges. *35*, 2954 (1902); *H. Erdtman*, Proc. Roy. Soc. (London), Ser. A *143*, 196 (1933).

[108] *J. Herzig, J. Pollak*, and *M. v. Bronnek*, Mh. Chem. *29*, 277 (1908); *H. Erdtman*, Svensk. kem. Tidskr. *47*, 230 (1935); *G. Pastuska*, Naturwissenschaften *48*, 457 (1961); *O. Th. Schmidt* and *W. Mayer*, Angew. Chem. *68*, 103 (1956).

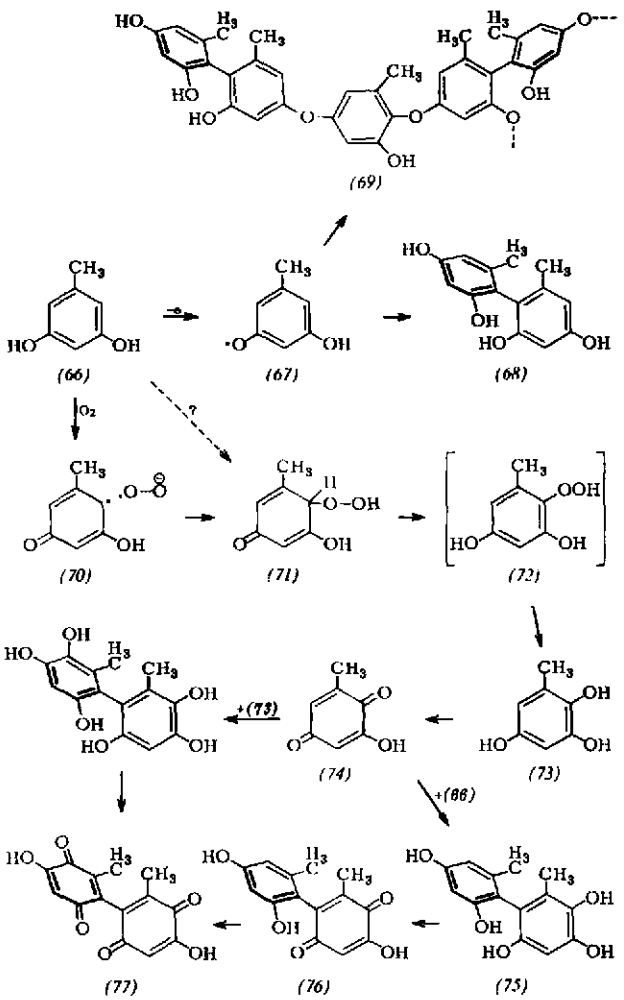
[109] *J. C. Salfeld*, Angew. Chem. *69*, 723 (1957).

[110] *L. Horner* and *W. Dürkheimer*, Z. Naturforsch. *14b*, 744 (1959); *L. Horner, K. H. Weber*, and *W. Dürkheimer*, Chem. Ber. *94*, 2881 (1961).

VI. Oxidation of Resorcinol Derivatives

The oxidation of resorcinol derivatives has been studied for a long time in connection with the formation of orceine and litmus dyes from orcinol. The structure of these products and the mechanism of their formation, however, have only recently been elucidated [111].

Since resorcinol cannot give rise to *o*- or *p*-quinonoid products on removal of two electrons, its behavior in the first oxidation step is that of a monophenol whose oxidation potential is lowered by the second hydroxy group.



Scheme 2. Products resulting from the oxidation of orcinol *(66)*.

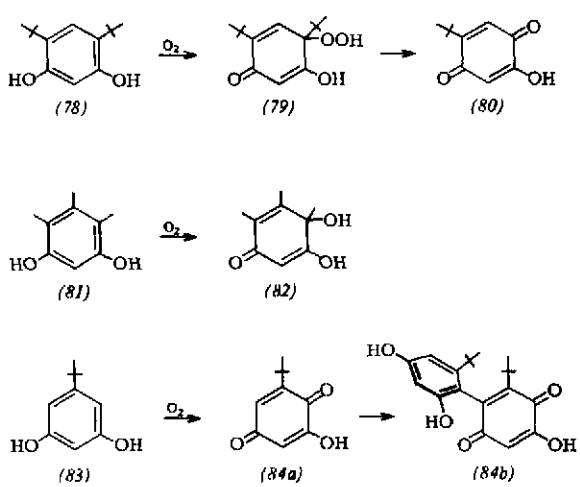
The oxidation of orcinol *(66)* with potassium ferricyanide in alkaline solution or with lead dioxide in benzene and its photo-dehydrogenation with benzophenone produce a mixture of polymers, *e.g. (69)*, containing only small percentages of dimer *(68)*. The formation of *(68)* can be considered as proof that radical *(67)* is involved in the reaction. Boiling of the polymers with sodium in pyridine causes them to undergo partial cleavage into *(66)* and *(68)*. This indicates that polymer *(69)* also contains ether linkages. The formation of products with rings coupled through the positions between the hydroxyl groups could not be detected [112].

Oxidation of orcinol *(66)* with oxygen affords a mixture of more than 50% of the dimeric monoquinone *(76)* plus the dimeric diquinone *(77)* [65].

The reaction course depicted in Scheme 2 is supported by the following considerations. The electrophilic attack of oxygen on the orcinol anion is rate-determining; this is indicated by the fact that, during autoxidation, only the final products can be identified spectroscopically. Whether a pair of electrons is transferred to the oxygen in the first step, with formation of the hydroperoxide derivative *(71)*, or whether at first only one electron changes its location, leading to the radical pair *(70)*, has not been resolved [113]. Free orcinol radicals *(62)*, are not formed as intermediates, as is indicated by the fact that the dimer *(68)* cannot be detected at any time in solution. The dimer *(68)* reacts with oxygen as fast as orcinol *(66)* does, and the presence of the latter can be readily determined chromatographically until the absorption of oxygen is complete. If potassium ferricyanide is added during the reaction, *(68)* can be found in the solution, and the oxygen absorption does not increase. This indicates that the orcinol radicals *(67)* react faster among themselves or with orcinol *(66)* to produce dimer *(68)* than with oxygen.

Since the rate of the autoxidation of orcinol corresponds approximately to its relative oxidation potential, it can be assumed that the rate-determining step is the same for all phenol oxidations and that here, too, only one electron is first transferred to the oxygen [114]. The transfer of the second electron in the radical pair *(70)* must take place rapidly before radical *(67)* is liberated and can dimerize to *(68)*.

The occurrence of the hydroperoxide intermediate *(71)* – although it cannot be demonstrated directly – is made probable by the formation of the highly stable hydroperoxide *(57)* and by the following reactions. Oxidation of 4,6-di-t-butylresorcinol *(78)* with air at –20 °C gives good yields of the hydroperoxide *(79)*, which is analogous to *(71)* [115] and which undergoes thermal decomposition to 2-t-butyl-5-hydroxybenzoquinone *(80)*, isobutylene, and other products. Whether the intermediates *(72)* and *(73)* are also formed in the case of orcinol has not been determined.



[111] Review: *H. Beecken, U. v. Gizycki, E. M. Gottschalk, H. Krämer, D. Maaßen, H.-G. Matthies, H. Musso, C. Rathjen*, and *U. I. Záhorszky*, Angew. Chem. *73*, 665 (1961).

[112] *H. Krämer*, Ph. D. Thesis, Universität Göttingen, 1960.

[113] *U. v. Gizycki*, Ph. D. Thesis, Universität Marburg, 1963.

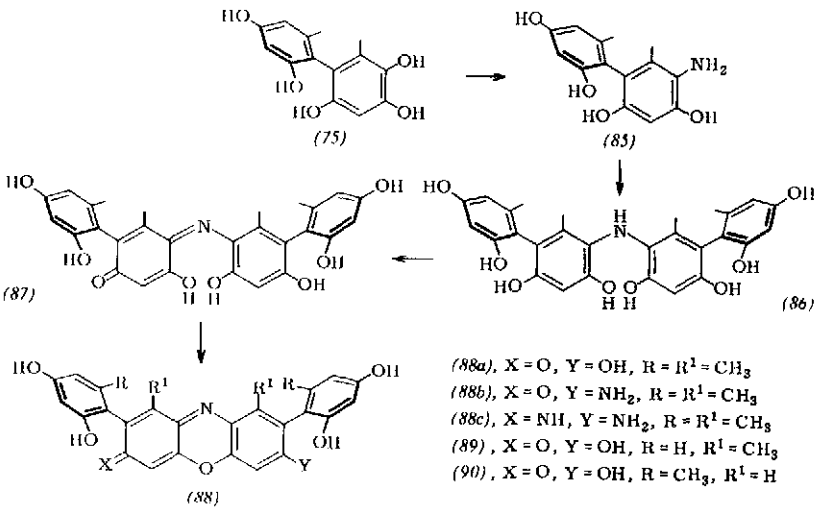
[114] See the discussion of the similar mechanism of the autoxidation of enolate ions to hydroperoxy ketones: *E. J. Bailey, D. H. R. Barton, J. Elks*, and *J. F. Templeton*. J. chem. Soc. (London) *1962*; 1578; *H. R. Gersman, H. J. Nieuwenhuis*, and *A. F. Bickel*, Proc. chem. Soc. (London) *1962*, 279; *G. A. Russell, E. G. Janzen, H. D. Becker*, and *F. J. Smentowski*, J. Amer. chem. Soc. *84*, 2652 (1962).

[115] *H. Musso* and *D. Maaßen*, unpublished results.

In the autoxidation of 4,5,6-trimethylresorcinol *(81)*, only the quinol *(82)* was isolated but in 60 % yield [116]. In the autoxidation of 5-t-butylresorcinol *(83)*, biphenyl coupling to give *(84b)* is sterically so hindered that it is possible to isolate the monomeric quinone *(84a)* [117]. On oxidation of orcinol, biphenyl coupling takes place by way of addition of the orcinol anion onto the hydroxyquinone *(74)* [118]. The dimeric diquinone *(77)* is formed both as a result of further oxidation of the monoquinone *(76)* and by addition of *(73)* onto *(74)* [113].

It should be noted that hydroquinones and pyrocatechols readily undergo enzymatic oxidation, but that derivatives of resorcinol and phloroglucinol are not attacked by tyrosinase [78]. Resorcinol and phloroglucinol inhibit the oxidation of *p*-cresol with a phenol oxidase from potatoes [119].

Autoxidation of resorcinol derivatives in the presence of ammonia affords orceine and litmus dyes. These consist of mixtures of 7-hydroxy- and 7-aminophenoxazones and 7-aminophenoxazimes of type *(88)* [111]. Ammonia



(88a), X = O, Y = OH, R = R^1 = CH_3
(88b), X = O, Y = NH_2, R = R^1 = CH_3
(88c), X = NH, Y = NH_2, R = R^1 = CH_3
(89), X = O, Y = OH, R = H, R^1 = CH_3
(90), X = O, Y = OH, R = CH_3, R^1 = H

participates in the autoxidation of resorcinol derivatives by replacing a hydroxy group of the hydroxyhydroquinone intermediate *(75)*, thus affording *(85)* and *(86)* [120]. After the diphenylamine derivative *(86)* has been oxidized to the indophenol *(87)*, ring closure to the orceine dye *(88)* can take place.

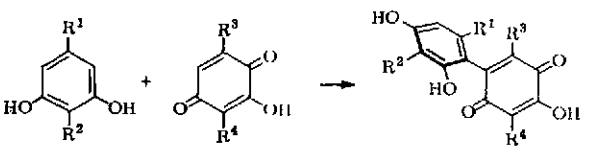
The autoxidation of resorcinol [121] and 2,5-dimethylresorcinol [122] proceeds analogously. On treatment with air, 2,4,5,2',4'-pentahydroxy-6,6-dimethylbiphenyl *(75)* in aqueous ammonia affords a 33 % yield of β- and γ-hydroxyorceine *(88a)*. Autoxidation of 2-amino-orcinol in the presence of resorcinol in aqueous sodium bicarbonate solution and autoxidation of hydroxyhydroquinone in ammoniacal orcinol solution afford 19 and 25 % yields, respectively, of the orceines *(89)* and *(90)* which are isomeric with respect to the methyl group. The syntheses of *(89)* and *(90)* show that the formation of the simple orceines by oxidation of resorcinol or orcinol in the presence of NH_3 is much slower than the oxidation of hydroxyhydroquinones to quinones, and slower than the addition of resorcinol, the introduction of nitrogen, and the ring closure [120] (also cf. Fig. 2). The introduction of the second and third nitrogen atoms into dyes *(88b)* and *(88c)* also takes place at the hydroquinone stage, *viz.* *(75)* and *(85)* [120].

The substitution of a hydroxyl group, by an amino group in the presence of air – apparently a free-radical process – was recently also reported for derivatives of pyrocatechol and pyrogallol [123].

VII. Addition of Phenols onto Quinones

Addition of a hydroxyquinone *(91)* to an alkaline solution of a resorcinol derivative or oxidation of a hydroxyhydroquinone with oxygen in the presence of resorcinol anions affords (hydroxyaryl)hydroxyquinones *(92)* sometimes in high yields (Table 1).

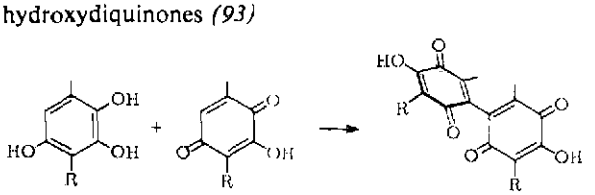
Table 1. Yields of (hydroxyaryl)hydroxyquinones *(92)*.



(91) *(92)*

R^1	R^2	R^3	R^4	*(92)* [%]	Ref.
H	H	H	H	21	[120]
CH_3	H	H	H	11	[120]
H	H	CH_3	H	28	[120]
CH_3	H	CH_3	H	92.5	[113]
$C(CH_3)_3$	H	$C(CH_3)_3$	H	32.5	[117]
CH_3	CH_3	CH_3	CH_3	90	[113]

Hydroxyquinones and hydroxyhydroquinones produce hydroxydiquinones *(93)*



(93a), R = H, 66% [113]
(93b), R = CH_3, 67% [113]

[116] *H. Musso, D. Maaßen*, and *D. Bormann*, Chem. Ber. *95*, 2837 (1962).

[117] *H. Musso* and *D. Bormann*, unpublished results.

[118] The coupling mechanism discussed in [111] is no longer valid, since a repetition of the experiments led to appreciably higher yields of the dimeric mono- and diquinones.

[119] *G. Schneider* and *S. Schmidt*, Hoppe-Seylers Z. physiol. Chem. *315*, 20 (1959).

[120] *U. I. Záhorszky*, Ph. D. Thesis, Universität Marburg, 1963.

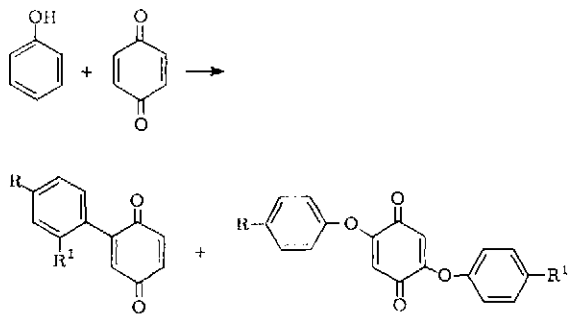
[121] *H. Musso, D. Maaßen, U. I. Záhorszky*, and *I. Seeger*, Chem. Ber. *96*, 1579 (1963).

[122] *H. Musso* and *C. Ruthjen*, Chem. Ber. *96*, 1593 (1963).

[123] *K. Ley*, Angew. Chem. *74*, 871 (1962); Angew. Chem. internat. Edit. *1*, 591 (1962).

Treatment of benzoquinone with phenol yields complicated mixtures from which, in addition to hydroxyquinone and polymers, the dimeric and trimeric compounds *(94a)* – *(94e)* have been isolated by chromatography and identified by comparison with authentic samples [113]. The yields are listed in Table 2. With phenoxide in benzene or dioxan, only polymers and hydroquinone are formed. Phenoxide in dimethylformamide or dimethyl sulfoxide affords *(94e)*.

Table 2. Yields obtained from the reaction of *p*-benzoquinone with phenol under various conditions.



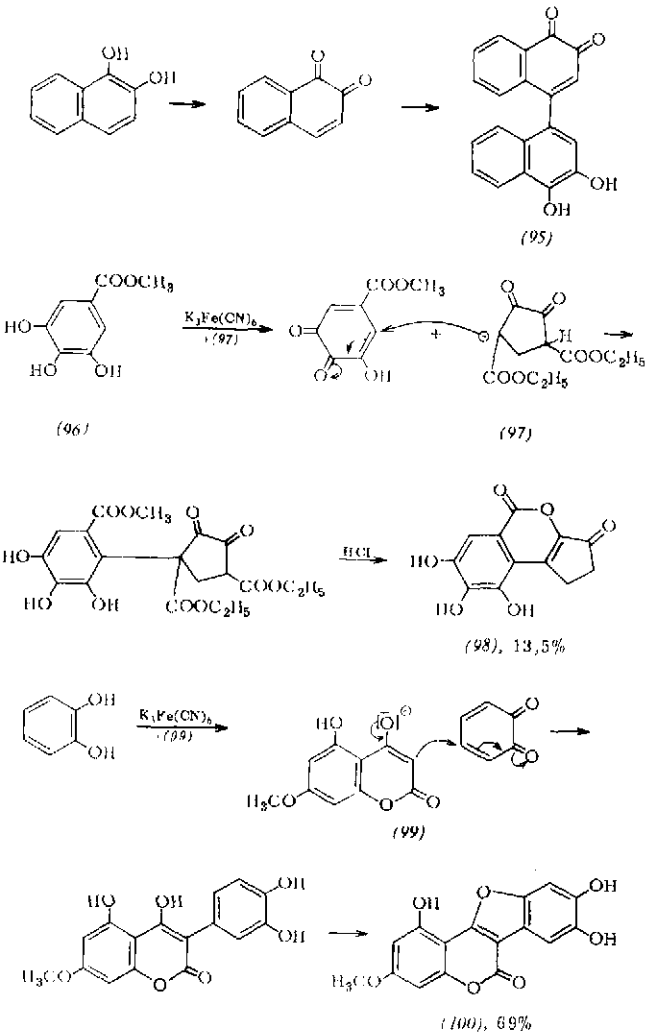
(94a), R = H, R^1 = OH
(94b), R = OH, R^1 = H
(94c), R = R^1 = H
(94d), R = OH, R^1 = H
(94e), R = R^1 = OH

Conditions	Yield [%]			
	(94a)	*(94b)*	*(94c)*	*(94d)*
At pH 10	–	4	–	0.5
At pH 7	4	8	5	3
In 20% H_2SO_4	20	2		
In BF_3/ether	16	7		

It is noticeable that phenols – in contrast to thiophenol and aniline – undergo substitution with quinone, preferably at the *o*- or *p*-positions. The reaction via the phenoxyl oxygen becomes appreciable only in neutral solution. These experiments are of interest with regard to the structure of the synthetic humic acid that is obtained by oxidation of hydroquinone. They show that ether linkages are also formed in the reaction of phenols with quinones, particularly in neutral solution [124].

The addition of a nucleophilic reagent onto a labile quinone is advantageously carried out by oxidizing the hydroquinone in the presence of the reagent. This is exemplified by the syntheses of the binaphthylquinone *(95)* [125], brevifolin *(98)* [126], and wedelolactone *(100)* [127] by addition of the anions *(97)* and *(99)* onto the *o*-quinone derived from methyl gallate *(96)* and onto *o*-benzoquinone, respectively. The *o*-quinones are prepared *in situ* by oxidation with potassium ferricyanide.

This scheme probably explains all, even intramolecular, C–C couplings occurring during the oxidation of phenols whereby one residue has an *o*- or *p*-hydroquinone structure.



(95)

(96)

(97)

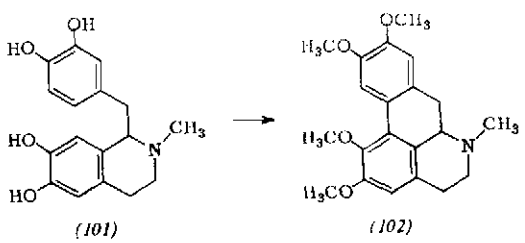
(98), 13,5%

(99)

(100), 69%

VIII. Syntheses of Natural Products

As early as 1911, *Gadamer* [128] attempted to explain the biosynthesis of glaucine *(102)* by assuming that laudanosoline *(101)* was dehydrogenated in plant cells.



(101) *(102)*

Later *Robinson* [129] and *Schöpf* [130] applied this concept in view of the synthesis of morphine. A few years ago, *Erdtman* and *Wachtmeister* [2] and *Barton* and *Cohen* [1] pointed out that the biosynthesis of numerous alkaloids, lichen substances, and metabolites

[124] Cf. *W. Eller*, Ber. dtsch. chem. Ges. *53*, 1473 (1920); *H. Erdtman*, Z. Pflanzenernähr., Düng., Bodenkunde *69*, 38 (1955); *W. Ziechmann*, Naturwissenschaften *48*, 456 (1961).

[125] *F. Straußß*, *O. Bernoully*, and *P. Mautner*, Liebigs Ann. Chem. *444*, 165 (1925).

[126] *H. W. Wanzlick*, Chem. Ber. *92*, 3006 (1959).

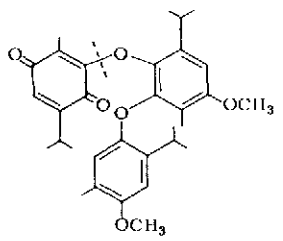
[127] *H. W. Wanzlick*, *R. Gritzky*, and *H. Heidepriem*, Chem. Ber. *96*, 305 (1963).

[128] *J. Gadamer*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *249*, 498 (1911).

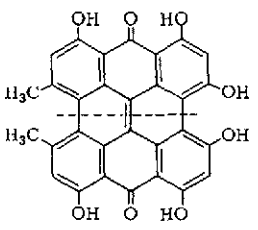
[129] *R. Robinson* and *S. Sugasawa*, J. chem. Soc. (London) *1931*, 3163; *1936*, 1079.

[130] *C. Schöpf* and *K. Tierfelder*, Liebigs Ann. Chem. *497*, 22, 47, 59 (1932).

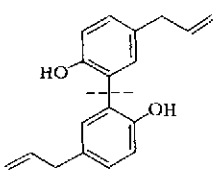
from microorganisms can often be explained by oxidation of phenols in the cell. Although it is extraordinarily difficult to prove that such oxidations really occur in the living cell, it has been possible within recent years to synthetize many complex natural products or closely related compounds by oxidation of phenols [131]. As oxidizing agents, ferric chloride or potassium ferricyanide in water, or manganese dioxide or lead dioxide in benzene or chloroform were found to be particularly suitable for this purpose. In formulae *(103)* to *(109)*, the bonds established by phenol oxidation are crossed by dashed lines. Further examples are podototarine [138], geodine [135], geodoxine [139] and diploicine [140].



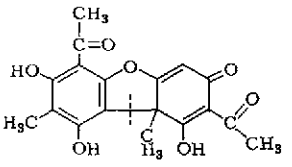
(103) [132]
3-Libocedroxy-
-thymoquinone



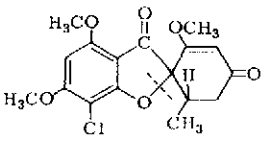
(104) [133]
Hypericin



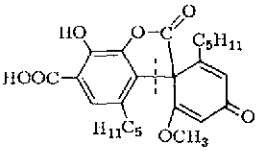
(105) [134]
Magnolol



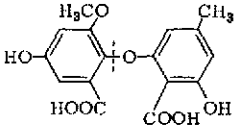
(106) [7]
Usnic acid



(107) [135]
Griseofulvin

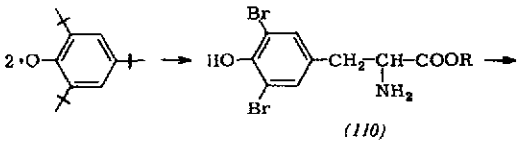


(108) [136]
Picrolichenic
acid

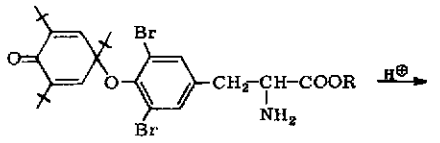


(109) [137]
Asteric acid

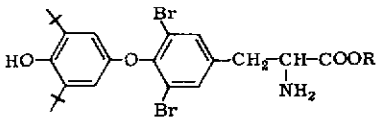
Model experiments for the biosynthesis of thyroxine have shown that treatment of dibromotyrosine *(110)* with the tri-t-butylphenoxy radical leads to the quinol *(111)*, which on acid catalysis, undergoes decomposition into the thyroxine analogue *(112)* and isobutylene [141].



(110)



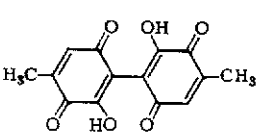
(111)



(112)

The numerous oxidation products obtained from coniferyl alcohol and their significance for the elucidation of the structure and mechanism of the formation of lignin will not be discussed in view of a comprehensive report on this subject recently published by *Freudenberg* [142]. For the synthesis of alkaloids by phenolic oxidation see [143].

Admittedly, oxidation of the postulated precursor occasionally does not lead to the natural product. For example, on autoxidation of orcinol in alkaline solution, not even a trace of phenicine *(113)* but only the quinones *(76)* and *(77)* are produced [65].



(113)

[131] Review: *E. E. v. Tamelen*, Fortschr. Chem. org. Naturstoffe *19*, 224 (1961); *J. R. Lewis*, Chem. and Ind. *1962*, 159.

[132] *E. Zavarin*, J. org. Chemistry *23*, 1198 (1958).

[133] *H. Brockmann*, Fortschr. Chem. org. Naturstoffe *14*, 141 (1957).

[134] *J. Runeberg*, Acta chem. scand. *12*, 188 (1958).

[135] *A. I. Scott*, Proc. chem. Soc. (London) *1958*, 195; *A. C. Day*, *J. Nabney*, and *A. I. Scott*, J. chem. Soc. (London) *1961*, 4067; *C. H. Kuo*, *R. D. Hoffsommer*, *H. L. Slates*, *D. Taub*, and *N. L. Wendler*, Chem. and Ind. *1960*, 1627; *D. Taub* and *N. L. Wendler*, Angew. Chem. *74*, 586 (1962); Angew. Chem. internat. Edit. *1*, 506 (1962).

[136] *T. A. Davidson* and *A. I. Scott*, Proc. chem. Soc. (London) 1960, 390.

[137] *R. F. Curtis*, *C. H. Hassell*, *D. W. Jones*, and *T. W. Williams*, J. chem. Soc. (London) *1960*, 4838.

[138] *S. M. Bocks* and *R. C. Cambie*, Proc. chem. Soc. (London) *1963*, 143; *S. M. Bocks*, *R. C. Cambie*, and *T. Takahashi*, Tetrahedron *19*, 1109 (1963); *C. P. Falshaw*, *A. W. Johnson*, and *T. J. King*, Chem. and Ind. *1963*, 451.

[139] *C. H. Hassal* and *J. R. Lewis*, J. chem. Soc. (London) *1961*, 2312.

[140] *C. J. Brown*, *D. E. Clark*, *W. D. Ollis*, and *P. L. Veal*, Proc. chem. Soc. (London) *1960*, 393.

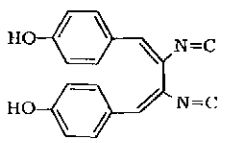
[141] *T. Matsuura* and *H. J. Cahnmann*, J. Amer. chem. Soc. *82*, 2050, 2055 (1960); *T. Matsuura* and *A. Nishinaga*, J. org. Chemistry *27*, 3072 (1962); *T. Matsuura*, *A. Nishinaga*, and *H. J. Cahnmann*, ibid. *27*, 3620 (1962).

[142] *K. Freudenberg*, Fortschr. Chem. org. Naturstoffe *20*, 41 (1962); *K. Freudenberg* and *H. Geiger*, Chem. Ber. *96*, 1265 (1963).

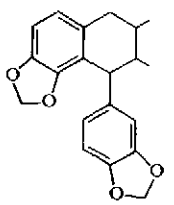
[143] *B. Franck*, Angew. Chem. *75*, 957 (1963); cf. *A. R. Battersby*, Proc. chem. Soc. (London) *1963*, 189; *A. R. Battersby*, *R. Binks*, *D. M. Foulkes*, *R. J. Francis*, *D. J. McCaldin*, and *H. Ramuz*, ibid. *1963*, 203; *D. H. R. Barton*, *G. W. Kirby*, *W. Steglich*, and *G. M. Thomas*, ibid. *1963*, 203.

IX. Conclusion

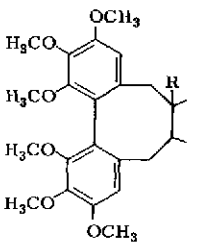
From the preceding review, it can be seen that the oxidation of phenols is of great interest in many areas of organic chemistry. The study of stable phenoxyl radicals, in particular, has contributed to an understanding of this reaction, although many details concerning the mechanism of this reaction and the electronic structure of the free phenoxyl radicals are still missing. Nevertheless, numerous interesting compounds will be synthetized by this method in the future as a result of the continuing discoveries of new natural products which may be envisioned as arising by phenolic oxidation, *e.g.* *(114)–(124)*.



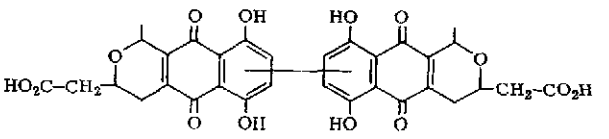
(114)
Xanthocillin [144]



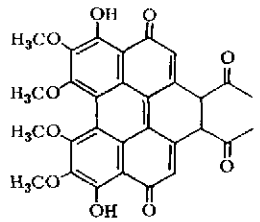
(115)
Otabin and other lignans [145]



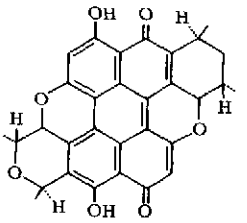
(116)
Schizandrin; R = OH [146]
Deoxyschizandrin; R = H [147]



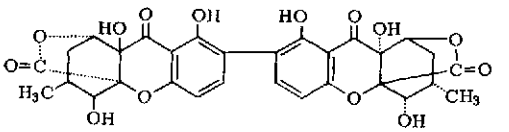
(121) [153]
Actinorhodine



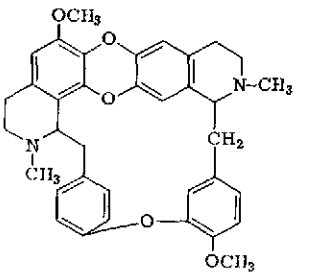
(117)
Elsinochrome A [148]
Phycarone [149]



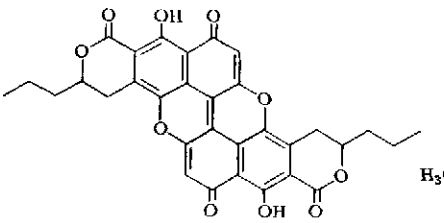
(118)
Erythroaphin [150]



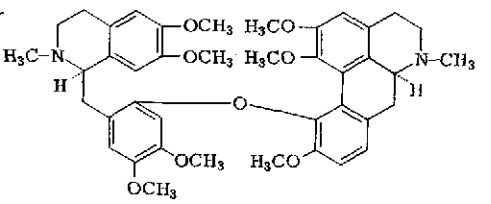
[154]
Ergoflavin



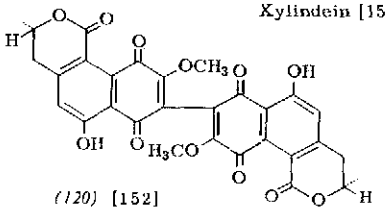
(123) [155]
Trilobine



(119)
Xylindein [151]



(124) [156]
Thalicarpine



(120) [152]
Xanthomegnin

Received, July 26th, 1963 [A 331/124 IE]
German version: Angew. Chem. *75*, 965 (1963)

[144] *I. Hagedorn* and *U. Eholzer*, Angew. Chem. *74*, 215 (1962); Angew. Chem. internat. Edit. *1*, 212 (1962).

[145] *R. Stevenson*, Chem. and Ind. *1962*, 270; *N. S. Bhacca* and *R. Stevenson*, J. org. Chemistry *28*, 1638 (1963).

[146] *N. K. Kochefkov*, *A. Khorlin*, *O. S. Chizkov*, and *V. I. Sceichenko*, Tetrahedron Letters *1961*, 730.

[147] *N. K. Kochefkov*, *A. Khorlin*, and *O. S. Chizhov*, Tetrahedron Letters *1962*, 361.

[148] *T. J. Batterham* and *U. Weiss*, Proc. chem. Soc. (London) *1963*, 89.

[149] *W. H. L. Hakeng*, *H. Copier*, and *C. A. Salemink*, Recueil Trav. chim. Pays.-Bas *82*, 322 (1963).

[150] *A. R. Todd*, Experientia *18*, 433 (1962).

[151] *G. M. Blackburn*, *A. H. Neilson*, and *A. Todd*, Proc. chem. Soc. (London) *1962*, 327.

[152] *G. Just*, *W. Day*, and *F. Blank*, Canad. J. chem. *41*, 74 (1963).

[153] *H. Brockmann*, *K. v. d. Merve*, and *W. Müller*, Naturwissenschaften 49, 130, 131 (1962).

[154] *J. W. ApSimon*, *J. A. Corran*, *N. G. Creasey*, *K. Y. Sim*, and *W. B. Whalley*, Proc. chem. Soc. (London) *1963*, 209; *J. D. M. Asher*, *A. T. McPhail*, *J. M. Robertson*, *J. V. Silverton*, and *G. A. Sim*, ibid. *1963*, 210.

[155] *Y. Inubushi*, Tetrahedron Letters *1962*, 1133.

[156] *S. M. Kupchen* and *N. Yokoyama*, J. Amer. chem. Soc. *85*, 1361 (1963).

Sulfidimines from Sulfoxides and N-Sulfinylsulfonamides

By Dr. G. Schulz and Prof. Dr. G. Kresze

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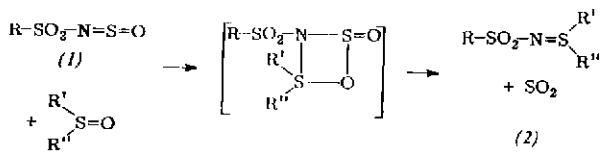
Like aldehydes and formamides, sulfoxides also react with *N*-sulfinylsulfonamides *(1)* in a kind of Wittig reaction; *N*-sulfonylsulfidimines *(2)* are formed, with evolution of SO_2.



(1) *(2)*

The reaction takes place especially easily with aliphatic sulfoxides – occasionally strongly exothermically – when the components are mixed at room temperature in an inert solvent such as benzene. The sulfidimines which are formed precipitate out some after only a short time – in crystalline form. In the case of aromatic sulfoxides, the components must be heated to 80 °C for several hours in benzene or to 100 °C without solvent; here the reaction products are less pure and are obtained in smaller yields.

The following *N*-sulfonylsulfidimines *(2)* were prepared:

R'	R''	R	Yield [%]	M.p. [°C]
CH_3	CH_3	CH_3	61	122–123
CH_3	CH_3	*p*-CH_3 C_6H_4	82	158–159
C_2H_5	C_2H_5	*p*-CH_3 C_6H_4	83	144–145
$-(CH_2)_4-$	–	CH_3	50	101
$-(CH_2)_4-$	–	*p*-CH_3 C_6H_4	58	135–136
CH_3	C_6H_5	CH_3	46	124–126
C_6H_5	C_6H_5	CH_3	38	91.5–92

Methylene-bis-*p*-toluenesulfonamide was isolated as the only crystalline product after heating methylsulfinylbenzene with *N*-sulfinyl-*p*-toluenesulfonamide at 100 °C without solvent. In boiling benzene, dibenzyl sulfoxide reacts with neither *N*-sulfinyl-*p*-toluenesulfonamide nor *N*-sulfinylmethanesulfonamide. Benzaldehyde is formed in both cases by heating to 130 °C without solvent.

Under the conditions examined by us (with and without solvent and at temperatures up to 100 °C), sulfoxides react with neither *N*-sulfinylaniline nor *N*-sulfinyl-*p*-nitraniline.

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A Cleavage of C=C Double Bonds with Hydroxylamine

By Dr. Ernst Schmitt

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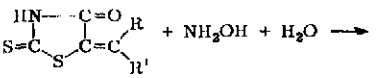
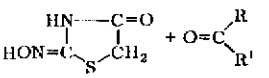
Rhodanines that are substituted in the 5-position react differently with hydroxylamine, depending on the kind of substituent present. Whereas 5-benzylidene- and 5-methylrhodanine give the corresponding 5-substituted 2-hydroxyimino-4-oxothiazolidines [1], cleavage of the C=C double bond is observed with 5-alkylidenerhodanines. With six of the compounds *(1)* studied, *viz.* 5-isopropylidene-, 5-cyclohexylidene-, 5-cyclopentylidene-, 5-(1-methyl-1-amylmethylene)-, 5-(1-methyl-1-isoamylmethylene)-, 5-(1-methyl-1-isobutylmethylene)-, and 5-diethylmethylenerhodanine, yields of 13–39 % 2-hydroxyimino-4-oxothiazolidine *(2)* were obtained after boiling with hydroxylamine hydrochloride and barium carbonate [2] in alcohol/water (5:1).



(1)



(2)

The carbonyl compound expected as second fragment was detected in the cases of the cyclohexylidene and 1-methyl-1-amylmethylene compounds as the oxime and dinitrophenylhydrazone, respectively. Of the 5-alkylidenerhodanines studied, only 5-cyclopentylidenerhodanine undergoes the normal reaction to yield 2-hydroxyimino-4-oxo-5-cyclopentylidenethiazolidine, m.p. 214–217 °C (decomp.).

Received, September 23rd, 1963 [Z 586/414 IE]
German version: Angew. Chem. 75, 1023 (1963)

[1] *N. M. Turkevich* and *O. P. Melnichuk*, Ukrain. Khim. Zhur. *16*, No. 4, 459 (1950); Chem. Abstr. *49*, 1012 (1955).

[2] *E. Mameli* and *L. Zorzi*, Farmaco (Pavia) Ed. sci. *9*, 691 (1954); Chem. Abstr. *49*, 6229 (1955).

Synthesis of 3-Substituted 2-Azaindolizine Derivatives

By Prof. Dr. K. Winterfeld and Dr. H. Franzke

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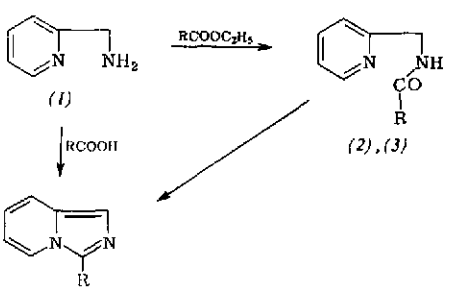
Direct condensation of suitable carboxylic acids with 2-picolylamine *(1)* in polyphosphoric acid yields 3-substituted 2-azaindolizines.

1. Propionic acid → 3-ethyl-2-azaindolizine *(4)*, colorless needles, m.p. 61 °C (cyclohexane), 58 % yield;

2. Lauric acid → 3-lauryl-2-azaindolizine *(5)*, colorless platelets, m.p. 69 °C (ethanol/cyclohexane), 72 % yield;

3. Benzoic acid → 3-phenyl-2-azaindolizine *(6)*, colorless needles, m.p. 110 °C (cyclohexane), 86 % yield.



(1) *(2), (3)* *(4) – (8)*

Carboxylic acids which undergo intermolecular condensation under the conditions of the condensing reaction (*e.g.* phenylacetic acid), react in the form of their ethyl esters with 2-picolylamine *(1)* to give *N*-(2-picolyl)carboxamides from which the 2-azaindolizines were obtained by subsequent condensation in polyphosphoric acid:

4. Ethyl phenylacetate → *N*-(2-picolyl)phenylacetamide *(2)*; colorless needles, m.p. 109 °C (ethanol), 79 % yield; converted into 3-benzyl-2-azaindolizine *(7)*, colorless needles, m.p. 80 °C (cyclohexane), 66 % yield.

5. DL-Ethyl mandelate → *N*-(2-picolyl)mandelamide *(3)*; colorless needles, m.p. 106 °C (methanol), 82 % yield; converted into 3-(α-hydroxybenzyl)-2-azaindolizine *(8)*; colorless platelets, m.p. 68 °C (cyclohexane), 37 % yield.
The solutions of *(4)* *(8)* show blue fluorescence.

Received, September 30th, 1963 [Z 591/420 IE]
German version: Angew. Chem. 75, 1101 (1963)

The Interaction of Dye Cations with Lewis Bases

By Prof. Dr. G. Scheibe, Dipl.-Chem. G. Buttgereit, and Dipl.-Chem. E. Daltrozzo

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Lewis bases |B—H and the cations of dyes $A^{\oplus}$ react reversibly to form stochiometric adducts $A-\overset{\oplus}{B}-H$ [1]:

(1) $A^{\oplus} + |B-H \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} A-\overset{\oplus}{B}-H + \Delta H \qquad \Delta H < 0$

Because of the interruption of the chromophoric system, the long-wave bands of the absorbtion spectrum disappear (isosbestic points!) [2]. Reaction (1) requires a measurable activation energy; the equilibria depend on temperature and concentration.

Small additions of amine to solutions of the dye in inert solvents, such as benzonitrile, acetone, and acetonitrile, cause disappearance of the long-wave bands, but Lewis bases, such as dimethyl sulfoxide, water, and alcohols, cause appreciable changes only when the base is used as solvent (*i.e.* in great excess). This is shown in Table 1 for Michler's hydrol blue (MH):

Table 1. Position and extinction of the 0→0-transition of the color band of MH-perchlorate at 20 °C.

Solvent	C_6H_5CN	CH_3COCH_3	CH_3CN	C_2H_5OH		H_2O	
$\varepsilon_{max}\times10^{-3}$	165	165	164	18	11	9.5	3.0
$\tilde{\nu}_{max}\times10^{-3}$ [cm^{-1}]	16.1	16.45	16.5	16.5	16.5	16.5	16.5
$c_{A^{\oplus}}\times10^{5}$ [mole/l]	independent			820	8.2	9.0	1.8

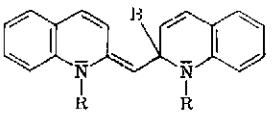
The equilibrium constants of Reaction (1) provide a measure of the formation of adducts. The reactivity of the bases falls off according to the following series for all the dyes investigated: piperidine, pyrrolidine, diethylamine, *N*-methylpiperidine > di-(β-hydroxyethyl)amine > water > ethanol > dimethyl sulfoxide. The ability of dyes to act as acceptor falls off along the series: diphenylmethane dyes (*e.g.* MH) > triphenylmethane dyes (crystal violet) > quinocyanines (pseudoisocyanines, quinoline red) > open-chain cyanines > pyridoquinocyanines > pyridocyanines.

If the base |B—H has a proton on the connecting heteroatom, a further equilibrium (2) is coupled to equilibrium (1). Both stages can be demonstrated by potentiometric pH-determination.

(2) $A-\overset{\oplus}{B}-H \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} A-B + H^{\oplus}$

The products A B can be isolated by extraction with nonpolar solvents; *e.g.* MH-ammonia, m.p. 174 °C; MH-piperidine, m.p. 156.5 °C; MH-pyrrolidine, m.p. 139 °C; MH-imidazole, m.p. 125–126 °C; MH-diethylamine, m.p. 114–115 °C; MH-methanol, m.p. 67–69 °C; MH-water (identical with the carbinol base), m.p. 100–101 °C. The stability of the adducts increases with the reactivity of the coreactant.

The ultraviolet absorbtion spectra of $A-\overset{\oplus}{B}-H$ and A–B are largely independent of the complexing base, and correspond to those of the residual chromophores, *e.g.* the left half of the molecule in *(1)*:



(1)

The original cations of the dyes may be obtained from A–B by addition of acids. Thus dyes with any desired anion may be formed.

Received, September 26th, 1963 [Z 587/415 IE]
German version: Angew. Chem. 75, 1023 (1963)

[1] *G. Scheibe* et al., Ber. Bunsenges. physik. Chem. *67*, 560 (1963); *W. Dilthey* and *R. Winziger*, already observed reversible lightening of triphenylmethane dyes with piperidine in 1926 [Ber. dtsch. chem. Ges. *59*, 1856 (1926)]; cf. also *R. Cernâtescu* and *M. P. Poni*, Bull. Sect. sci. Acad. rom. *24*, 132 (1941); *F. Kröhnke* et al., Liebigs Ann. Chem. *600*, 176 (1956), called attention to the 2- or 4-addition of piperidine onto cycloimmonium salts.

[2] In the meantime, *G. Briegleb* et al., Angew. Chem. *75*, 671 (1963); Angew. Chem. internat. Edit. *2*, 545 (1963), have reported on similar adducts of *N*-bases and cycloimmonium cations.

Synthesis of Derivatives of 1,2,6-Thiadiazine-1,1-dioxide

By Dr. Rolf Zimmermann and H. Hotze

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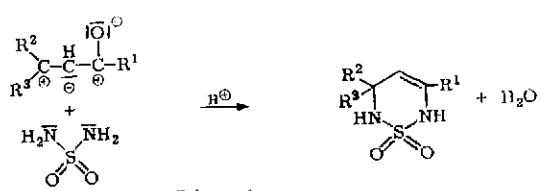
α,β-Unsaturated ketones react with sulfuryl amide in alcoholic solutions that have been saturated at 0 °C with gaseous hydrogen chloride according to Scheme 1; ring-closure occurs to yield derivatives of 1,2,6-thiadiazine-1,1-dioxide. The reaction is carried out advantageously by



Scheme 1

refluxing for 1–2 hours, or by stirring at 20–25 °C for 15–20 hours. The cyclization proceeds particularly smoothly with *p*-halogenobenzylideneacetophenones. Examples are summarized in Table 1.

Table 1. Examples of reactions according to Scheme 1.

R^1	R^2	R^3	M.p. [°C]	Yield [%]
CH_3	CH_3	CH_3	141	80.5
C_6H_5	H	C_6H_5	164–165	49
p-Cl–C_6H_4	H	C_6H_5	201	82
C_6H_5	H	*p*-Cl–C_6H_4	212–213	79.7
C_6H_5	H	*p*-H_3CO–C_6H_4	199–200	79.2
p-Cl–C_6H_4	H	*p*-H_3CO–C_6H_4	210	42
3,4,5-Trimethoxyphenyl	H	*p*-Cl–C_6H_4	213–214	41

Maleic acid or its esters are isomerized to fumaric esters by sulfuryl amide; cyclization has so far not been achieved.

Received, October 1st, 1963 [Z 592/418 IE]
German version: Angew. Chem. 75, 1025 (1963)

Reactions of Activated Methyl Groups Attached to Heterocycles

By Prof. Dr. H. Bredereck and Dr. G. Simchen

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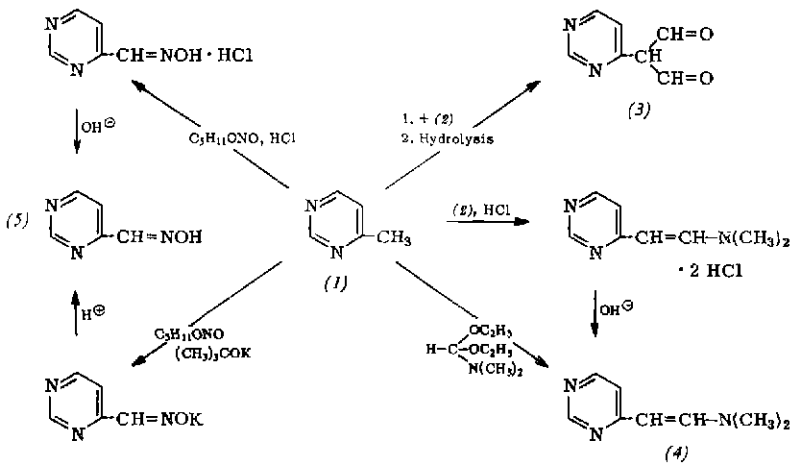
Hitherto, activated methyl groups attached to heterocycles other than quaternary bases could not be formylated (see, for example [1]).

Arnold recently reported the reaction of γ-picoline with dimethylformamide/acid chloride complexes to give (4-pyridyl)malondialdehyde [2]. We have obtained (4-pyrimidyl)-malondialdehyde *(3)* by the reaction of 4-methylpyrimidine *(1)* with 2 moles of dimethylformamide/phosgene complex *(2)*, and subsequent hydrolysis.

In contrast to the reaction of γ-picoline, however, the monoformylation product, *viz.* 4-(β-dimethylaminovinyl)pyrimidine *(4)*, was also successfully obtained in 80 % yield from the reaction of *(1)* with *(2)* in the presence of molar quantities of HCl. Compound *(4)* is also formed in 70 % yield from *(1)* and dimethylformamide diethylacetal.



As a further example of an electrophilic agent, we treated isoamylnitrite with *(1)* in the presence of molar quantities of either potassium t-butoxide or HCl in ethanol, and obtained the oxime of pyrimidine-4-carboxaldehyde *(5)* in 40 and 80 % yield, respectively. This is the first direct conversion of a methyl group on a heterocyclic nucleus into the aldoxime.

We shall describe the free pyrimidine-4-carboxaldehyde and other heterocyclic aldehydes in a later communication.

Received, October 4th, 1963 [Z 594/426 IE]
German version: Angew. Chem. *75*, 1102 (1963)

[1] *W. Pfleiderer* and *H. Mosthaf*, Chem. Ber. *90*, 728 (1957).
[2] *Z. Arnold*, Collect. czechoslov. chem. Commun. *28*, 863 (1963).

The Reaction of α,β-Unsaturated Ketones with Thiourea

By Dr. Rolf Zimmermann

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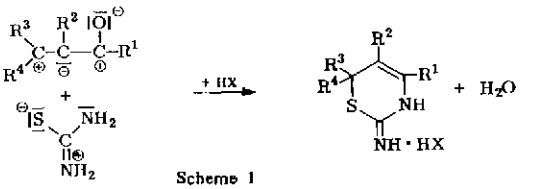
Whereas the interaction of mesityl oxide and isothiuronium chloride yields open-chain isothiuronium salts [1], that of α,β-unsaturated ketones and β-hydroxy ketones with thiourea produces derivatives of 2-iminotetrahydro-1,3-thiazine (Scheme 1). This general reaction is carried out in alcoholic solution, saturated with hydrogen halide at room or reflux temperature, and is illustrated by the examples given in Table 1.

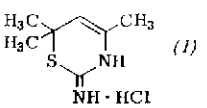


Scheme 1

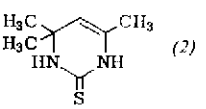
Table 1. Examples of reactions according to Scheme 1.

R^1	R^2	R^3	R^4	X	M.p. [°C]	Yield [%]
CH_3	H	CH_3	CH_3	Cl	199–200	82
CH_3	H	CH_3	CH_3	Br	192–193	50.6
CH_3	H	H	C_6H_5	Cl	124	75
CH_3	CH_3	H	C_6H_5	Cl	235–236	72
CH_3	CH_3CO	H	C_6H_5	Br	150	60
C_2H_5	H	H	C_6H_5	Cl	228	72

Thiourea reacts with α,β-unsaturated ketones, *e.g.* mesityl oxide, in aqueous hydrochloric acid in both its normal and mesomeric forms, yielding about 90 % of total yield as 2-imino-4,6,6-trimethyltetrahydro-1,3-thiazine hydrochloride *(1)*, m.p. 199–200 °C, and about 10 % as 2-thioxo-4,6,6-trimethyltetrahydropyridine *(2)*, m.p. 242 °C.



(1)



(2)

Received, October 1st, 1963 [Z 593/419 IE]
German version: Angew. Chem. *75*, 1025 (1963)

[1] *J. Willems* and *A. Vandenberghe*, Ind. chim. belge *1958*, 467.

Sugar Esters of Nitrogenous Fatty Acids [1]

By Dr. R. M. Ismail and Dr. H. Simonis [*]

Forschungslaboratorien der Firma H. J. Zimmer, Frankfurt/Main (Germany)

We have prepared sugar esters of nitrogenous fatty acids in almost quantitative yield by transesterification of the methyl esters with sucrose. The resultant mixture of mono- and di-esters consists mainly of monoester (see last column of Table 1). The introduction of hydrophilic groups into the fatty acid residue increases the solubility of these detergents in water. These sugar esters are characterized by high surface activity and complete bacterial degradability.

Table 1. Properties of sugar esters of substituted stearic acids (SSE)

Compound	M.p. [°C]	Surface tension [a] [dyne/cm]	Wetting power [b] [sec]	N-content [%]	
				Found	Calc. [c]
12-Amino-SSE	Paste	32	41	2.54	2.26
12-Oximino-SSE	63—65	33	35	2.20	2.20
9-Hydroxy-10-dimethylamino-SEE + 10-Hydroxy-9-dimethylamino-SSE	Paste	34	26	2.26	2.13
9-Acetamido-SEE + 10-Acetamido-SEE	60—62	33	32	2.36	2.18

[a] Measured at 20 °C in 0.15 % solution (stalagmometer according to Prof. *Traube*).
[b] Measured according to DIN 53901 in distilled water at 20 °C (compared to Marseilles soap [25 sec]).
[c] Based on 100 % monoester.

We have prepared, *inter alia*, methyl aminostearate and oximinostearate by isomerization of methyl ricinoleate [2] to methyl ketostearate, followed by oximation [3] and reduction [4], respectively. Hydroxydimethylaminostearic acid was obtained by cleavage of the oxiran ring [5] of epoxystearic acid with dimethylamine. Addition of acetonitrile onto the double bond of oleic acid [6] gave acetamidostearic acid. The properties of the sugar esters prepared are shown in Table 1.

Received, October 7th, 1963 [Z 595/427 IE]
German version: Angew. Chem. 75, 1102 (1963)

[*] With the assistance of *B. Gellenbeck* and *W. Bärnthaler*.

[1] Communication No. 2 on degradable detergents. Communication No. 1: *H. Simonis* and *R. M. Ismail*, Angew. Chem. 75, 791 (1963); Angew. Chem. internat. Edit. 2, 549 (1963).

[2] French Patent 1043797 (Oct. 12th, 1953) Société Organico.

[3] *J. Ross, A. J. Gebhart*, and *J. F. Gerecht*, J. Amer. chem. Soc. 71, 282 (1949).

[4] *T. Wieland* and *R. M. Ismail*, Chem. Ber. 95, 500 (1962).

[5] *D. Swern* and *T. W. Findley*, J. Amer. chem. Soc. 74, 6139 (1952).

[6] *E. T. Row* and *D. Swern*, J. Amer. chem. Soc. 75, 5479 (1953).

Nitrosyl(triphenylphosphine)iridium Compounds

By Prof. Dr. L. Malatesta, Dr. M. Angoletta, and Dr. G. Caglio

Centro Nazionale di Chimica dei Composti di Coordinazione e Metallo-Organici del C.N.R., Istituto di Chimica Generale e Inorganica dell'Università di Milano (Italy)

Dihydridotris(triphenylphosphine)iridium perchlorate $[IrH_2(PPh_3)_3]ClO_4$ [1], reacts with NO to give dinitrosylbis(triphenylphosphine)iridium perchlorate *(1)*, a very stable diamagnetic compound which is soluble with complete dissociation in organic solvents. With lithium halides in ethanol, *(1)* gives the halogenodinitrosylbis(triphenylphosphine)iridium compounds *(2)*, *(3)*, and *(4)*, which decrease in stability from the iodide to the chloride; these compounds are non-electrolytes and are diamagnetic. Reaction of hydrogen halides with *(1)* yields the non-electrolytic, diamagnetic dihalogenonitrosylbis(triphenylphosphine)iridium compounds, *(5)*, *(6)*, and *(7)*. These are also slowly formed spontaneously by dissolving *(2)*, *(3)*, and *(4)* in organic solvents.

Excess bromine converts *(1)* into tribromonitrosylbis(triphenylphosphine)iridium *(8)*, an almost insoluble paramagnetic (μ = 1.34 B.M. at 25 °C) non-electrolyte; excess chlorine gives trichloronitrosylbis(triphenylphosphine)iridium perchlorate *(9)*, which is a diamagnetic electrolyte. When refluxed with ethanolic PPh_3, *(1)* gives nitrosyltris(triphenylphosphine)iridium *(10)*, whose cobalt and rhodium homologues are already known.

NO and $IrH(CO)(PPh_3)_3$ react to form a mixture of carbonylnitrosylbis(triphenylphosphine)iridium *(11)* and a stable black crystalline paramagnetic (μ = 1.4 B.M.) solid, with an analytical composition which corresponds to dinitrosyl(triphenylphosphine)iridium *(12)*. The same compound was obtained in better yields from $IrH_3(PPh_3)_2$ and NO. Further studies on *(12)* are in progress.

The properties of *(1)*–*(12)* are recorded in Table 1. The very low infrared absorption frequencies of *(2)*–*(7)* are very interesting, as the 1500–1550 cm^{-1} range had so far been considered to be characteristic for bridging NO [2].

Table 1. Some properties of nitrosyl(triphenylphosphine)iridium compou

Compound	Formula L = $P(C_6H_5)_3$	M.p. [°C]	Color	ν [cm^{-1}]
(1)	$[Ir(NO)_2L_2]ClO_4$	225	violet	1715—1760
(2)	$IrCl(NO)_2L_2$	—	beige	1495—1540
(3)	$IrBr(NO)_2L_2$	—	light-brown	1500—1540
(4)	$IrI(NO)_2L_2$	181—182	brown	1500—1550
(5)	$IrCl_2(NO)L_2$	229—230	brown	1560
(6)	$IrBr_2(NO)L_2$	252—253	red-brown	1560
(7)	$IrI_2(NO)L_2$	244—245	red-brown	1560
(8)	$IrBr_3(NO)L_2$	242—243	maroon	1730
(9)	$[IrCl_3NOL_2]ClO_4$	145—147	beige	1925
(10)	$Ir(NO)L_3$	155—156	orange	1615
(11)	$Ir(NO)(CO)L_2$	168	orange	1940(CO)—16
(12)	$Ir(NO)_2L$	160—161	black-violet	1645—1680

The molecular weights of the halogenonitrosyl compounds could not be determined, because *(2)*, *(3)*, and *(4)* are unstable in solution, and *(5)*, *(6)*, and *(7)* are almost insoluble. The presence of NO bridges can however be excluded for *(2)*, *(3)*, and *(4)*, at least, as two NO bridges would bring the coordination number of the iridium(-I) up to the improbable value of seven.

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German version: Angew. Chem. 75, 1103 (1963)

[1] *M. Angoletta*, Gazz. chim. ital. 92, 811 (1962).

[2] *R. B. King* and *M. B. Bisnette*, J. Amer. chem. Soc. 85, 2527 (1963).

Thermal Equilibrium between cis-1,2-Divinylcyclopentane and cis,cis-1,5-Cyclononadiene

By Prof. Dr. E. Vogel, Dr. W. Grimme, and Dipl.-Chem. E. Dinné

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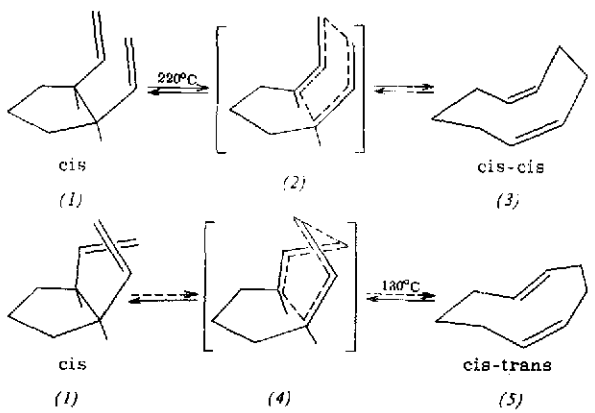
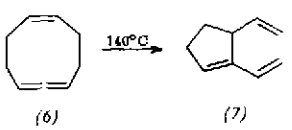
Above 300 °C, *cis*-1,2-divinylcyclopentane *(1)* undergoes reversible *cis-trans*-isomerization [1]. We have further found that at 220 °C, *(1)* gives an equilibrium mixture containing ca. 5 % *cis,cis*-cyclonona-1,5-diene *(3)*, produced by Cope rearrangement. Compound *(3)*, b.p. 50 °C/12 mm, n_D^{20} = 1.4921

(intense *cis*-double bond absorption at 740 cm^{-1}) was synthetized independently by reduction of *cis*-cyclonona-1,2,6-triene *(6)* [2] with sodium in liquid ammonia [3]. When *(3)* was heated to 220 °C, it gave an equilibrium mixture identical with that formed from *(1)*.

The formation of *(3)* indicates that the Cope rearrangement of *cis*-1,2-divinylcyclopentane proceeds via a six-centred transition state *(2)* [4] in which the carbon atoms of the diallyl system are arranged similar to a boat-form. A chair-type, four-centred transition state *(4)* would be expected to give *cis,trans*-cyclonona-1,5-diene *(5)* as rearrangement product; according to Dreiding and Stuart models, *(5)* is more strained than the *cis,cis*-isomer *(3)*.



Compound *(5)*, $n_D^{20} = 1.4949$ (*cis*- and *trans*-double bond absorptions at 720 and 971 cm^{-1}, respectively) [5] was prepared from both homopseudopelletierine (analogous to the preparation of the labile homologue *cis,trans*-cycloocta-1,5-diene) and 6-dimethylamino-*cis*-cyclononene (by Hofmann degradation) [6]. Like its eight-membered homologue, the new hydrocarbon tends to polymerize; it can nevertheless



be isomerized in the gas phase at 130 °C under reduced pressure. Like the process starting from *(3)*, this gave gas-chromatographically pure *(1)* [7].

As is the case with an isocyanate group [8], the allene system can also take part in a valence isomerization of the type of the Cope rearrangement. In a reaction analogous to the rearrangements of *(3)* and *(5)*, *(6)* isomerizes at 140 °C in the gas phase to give 1,5-divinylcyclopentene *(7)*, b.p. 53 °C/125 mm, $n_D^{20} = 1.4972$, as sole product.

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German version: Angew. Chem. *75*, 1103 (1963)

[1] *E. Vogel, K.-H. Ott*, and *K. Gajek*, Liebigs Ann. Chem. *644*, 172 (1961).

[2] *L. Skatteböl*, Tetrahedron Letters *5*, 167 (1961).

[3] This reduction was also effected by *D. Devaprabhakara* and *P. D. Gardner*, J. Amer. chem. Soc. *85*, 648 (1963).

[4] Cf. *W. v. E. Doering* and *W. R. Roth*, Tetrahedron *18*, 67 (1962).

[5] We have not yet had sufficient substance available for an accurate boiling-point determination.

[6] We obtained this amine from the *cis*-cyclononen-6-one described by *D. Devaprabhakara* and *P. D. Gardner*, J. Amer. chem. Soc. *85*, 1458 (1963).

[7] For the analogous isomerization of cyclodeca-1,5-dienes see *C. A. Grob, H. Link*, and *P. W. Schiess*, Helv. chim. Acta *46*, 483 (1963); *G. Wilke*, Angew. Chem. *75*, 10 (1963); Angew. Chem. internat. Edit. *2*, 105 (1963).

[8] *E. Vogel*, Angew. Chem. *74*, 829 (1962); Angew. Chem. internat. Edit. *2*, 1 (1963).

Cyclopentadienone-hydrazone

By Prof. Dr. K. Hafner and cand. chem. K. Wagner

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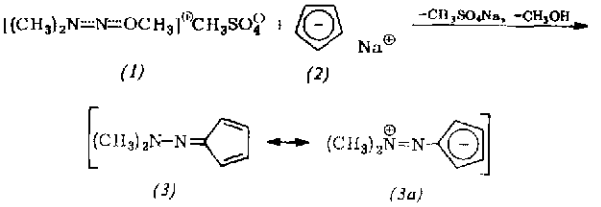
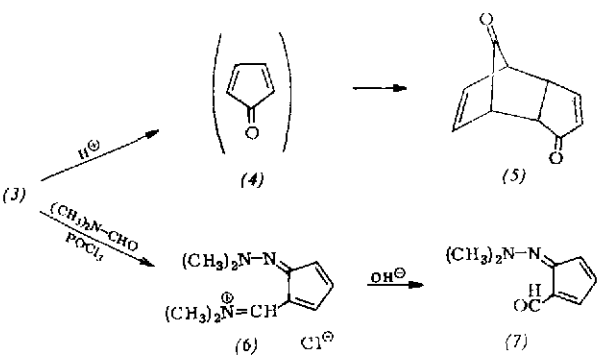
Alkylation of dimethylnitrosamine with dimethyl sulfate affords trimethylnitrosimmonium methylsulfate *(1)* [1]. This compound reacts with cyclopentadienylsodium *(2)* in tetrahydrofuran to give monomeric cyclopentadienone *N,N*-dimethylhydrazone *(3)*, orange leaflets, m.p. 14 °C, b.p. 107–108 °C/10 mm, λ_{max} (log ε) = 267.7 (3.31), 326.5 (4.41) mμ in n-hexane.



Compound *(3)* is the first cyclopentadienone derivative unsubstituted in the five-membered ring that is stable as the monomer. It can be distilled *in vacuo* without decomposition, and even at 200 °C shows no tendency to dimerize or to react with dienophiles. Its dipole moment of 3.3 D indicates definite participation of the dipolar structure *(3a)* in the ground state of this aza-analogue of 6-dimethylaminofulvene [2].

Hydrolysis of *(3)* with 2N H_2SO_4 leads immediately via *(4)* to dimeric cyclopentadienone *(5)* [3]. Electrophilic reagents substitute *(3)* in the five-membered ring. For example, Vilsmeier formylation of *(3)* with dimethylformamide and



phosphorus oxychloride yields the stable aldehyde *(7)*, orange needles, m.p. 65 °C, λ_{max} (log ε) = 251.8 (4.18), 373.5 (4.35) mμ in methanol, via the immonium salt *(6)*, which can be isolated as its perchlorate, orange needles, m.p. 135 °C (decomp.).

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German version: Angew. Chem. *75*, 1104 (1963)

[1] Cf. *S. Hünig* et al., Angew. Chem. *75*, 476 (1963); Angew. Chem. internat. Edit. *2*, 327 (1963).

[2] *K. Hafner* et al., Angew. Chem. *75*, 35 (1963); Angew. Chem. internat. Edit. *2*, 123 (1963).

[3] *K. Hafner* and *K. Goliasch*, Chem. Ber. *94*, 2909 (1961); *C. H. De Puy* et al., J. Amer. chem. Soc. *81*, 4629, 4920 (1959).

Light Absorption and Relative Electron Densities of Carbocyanine Dyestuffs

By Dr. S. Dähne and Dr. J. Ranft [*]

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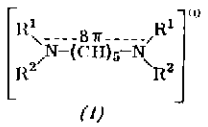
The relative electron densities at the α-methylene protons of simple pentamethine dyestuffs *(1)* decrease with increasing bathochromic shift of the longest-wavelength

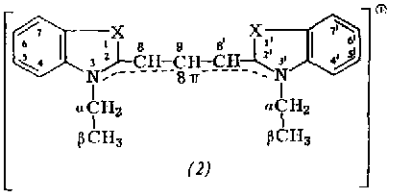


(1)

(1a): $R^1 = R^2 = C_2H_5$

R^1, R^2 = Alkyl groups which may also be attached together as part of a pyrrolidine or a piperidine ring; *(1a)*: $R^1 = R^2 = C_2H_5$.

electron excitation bands [1]. This relationship is largely confirmed by the proton-resonance spectra of the carbocyanine dyestuffs *(2)* which exhibit considerably greater variations in light absorption.



(2)

(2a): X = O
(2b): X = S
(2c): X = Se
(2d): X = –CH=CH–

The chemical shifts determined at 100 Mc/sec [2], which are a measure of the relative electron densities at the nucleus, are given in Table 1 together with the positions of the longest-wavelength electron excitation bands of the appropriate dyestuffs.

Table 1. Correlation between the chemical shifts τ and the position of the longest-wavelength electron excitation bands (λ_{max}) for carbocyanine dyestuffs.

Dyestuff	λ_{max} [mμ]	τ[ppm] [a] of the 3,3'-α-methylene protons	τ[ppm] of the 8,8'-methine protons	τ[ppm] of the 9-methine protons
(1a)	415.5	6.53	4.23	2.39
(3) [b]	445.5	6.36	3.90	2.63
(2a)	485.0	5.71	3.88	1.70
(2b)	559.0	5.41	3.36	2.21
(2c)	570.0	5.64	3.14	2.19
(2d)	605.0	5.55	3.46	1.31

[a] Based on τ for tetramethylsilane = 10.0.
[b] *(3)* = 3,3'-diethylthiazolidinocarbocyanine.

Remarkably, the relative electron densities at the 8,8'- and 9-methine protons diminish in the same order as those at the 3,3'-α-methylene protons, but with greater irregularity. It must be assumed that the electron densities at the remaining atoms (1,1'-, 2,2'-, or 3,3'-), which are part of the chromophoric system, are increased to a greater or lesser extent with increasing bathochromicity. This result is in agreement with the relationship between the light absorption and the basicity of the cyanine dyestuffs, discovered by *G. Scheibe* et al. [3,4], as an increased electron density at a given site corresponds to an increased basicity. However, *Scheibe*'s suggestion [4] that the increased basicity is localized at the 8- and 8'-methine carbon atoms is not confirmed for these dyes.

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German version: Angew. Chem. *75*, 1175 (1963)

[*] Present address: CERN, Geneva (Switzerland).

[1] *S. Dähne* and *J. Ranft*, Z. physik. Chem. (Leipzig), in the press; *S. Dähne*, Mber. dtsch. Akad. Wiss. *5*, 567 (1963).

[2] A detailed account of the proton-resonance spectra of the dyestuffs, and their interpretation will appear in Z. physik. Chem. (Leipzig). We would like to take this opportunity to express our sincere thanks to Dr. *A. Malera*, Research Laboratory, Varian AG. Zurich (Switzerland), who determined the proton-resonance spectra.

[3] *G. Scheibe* and *D. Brück*, Z. Elektrochem. Ber. Bunsenges. physik. Chem. *54*, 403 (1950).

[4] *G. Scheibe*, Chimia *15*, 10 (1961).

The Preparation of Quinolones by Condensation of Acetylenecarboxylic Esters with Aromatic Amines

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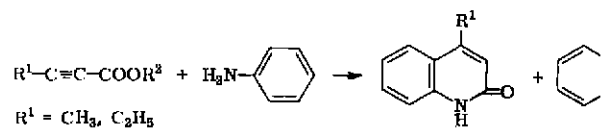
When α-acetylenic esters are heated without solvent at 230 to 250 °C for 10–15 min with aromatic amines in the presence of a small amount of cuprous chloride or cuprous oxide, 10–20 % 2-quinolones and 60–70 % 4-quinolones are formed. These can be separated by their different behaviors towards alkali.



$R^1 = CH_3$, C_2H_5

(1)

Table 1. 2-Quinolones *(1)* and 4-quinolones *(2)*.

R^1	*(1)* M.p. [°C]	*(1)* Yield [%]	*(2)* M.p. [°C]	*(2)* Yield [%]
3,4-Methylenedioxyphenyl	297	68	289 (290–291 [1])	14
Phenyl	252 (253–254 [2])	70	259 (259–260 [2])	20
n-Hexyl	128–129	60	139	10

Received, November 6th, 1963 [Z 612/439 IE]
German version: Angew. Chem. *75*, 1203 (1963)

[1] *H. R. Arthur* and *L. Y. S. Loh*, J. chem. Soc. (London) *1961*, 4360.

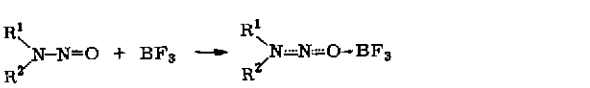
[2] *Ch. H. Hauser* and *G. A. Reynolds*, J. Amer. chem. Soc. *70*, 2402 (1948).

Nitrosamine Boron Trifluoride Complexes [1]

By Priv.-Doz. Dr. D. Klamann and Dr. W. Koser

ESSO-Forschungslaboratorien, Hamburg-Harburg (Germany)

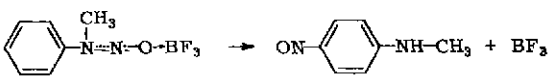
On mixing equimolar solutions of aliphatic nitrosamines and boron trifluoride etherate, or on passing gaseous boron trifluoride into solutions of the nitrosamines in ether or benzene at room temperature or 0 °C, colorless, crystalline complexes of 1:1 composition are obtained. The *N*-nitrosamines can be recovered from these complexes with alkali.



R^1 = alkyl, aryl; R^2 = alkyl; $R^1 + R^2$ = cyclic residue

The stability of the BF_3-nitrosamine complexes increases with the electron-donating properties of the residues attached to the amino nitrogen and thereby, according to theory, with increasing electron density of the >N–N=O-system. Provided moisture is excluded, the BF_3-complexes of aliphatic and heterocyclic nitrosamines can be kept for months without alteration. The nitrosamine of *N*-methylaniline forms a quantitative yield of a bright yellow BF_3-complex; however, this rearranges after a short time into *p*-nitroso-*N*-methylaniline with formation of a dark green color. The N–N bond is so strongly influenced by the benzene ring that the NO-

group is released from the boron trifluoride and subsequently reacts according to the Fischer-Hepp "rearrangement" mechanism:



The complex of diphenylnitrosamine is not isolable; on mixing the nitrosamine and boron trifluoride etherate solution, the reaction mixture immediately turns deep blue-black at −20 °C even with strictest exclusion of moisture, and a small amount of black precipitate separates.

The boron trifluoride complexes of the nitrosamines all show a characteristic infrared band at 1500–1560 cm^{-1} (cf. Table 1); this lies in the region of the band between 1540 and 1575 cm^{-1} assigned by *Hünig* [2] to the mesomeric system $\rangle N\cdots\overset{\oplus}{N}{=}O{-}R]X^{\ominus}$. From spectroscopic measurements of the pK values, the *N*-nitrosamines are protonated predominantly on the oxygen [3]. The *O*-alkylation of the *N*-nitrosamines [2] and the spectroscopic proof of complex formation at the oxygen atom in Pd(II) complexes of *N*-nitrosamines [4] lead to the conclusion that the oxygen atom likewise serves as donor atom in the BF_3-nitrosamine complexes.

Table 1. Nitrosamine-BF_3 complexes $R^1R^2N{-}NO\cdots BF_3$

R^1	R^2	Fp [°C] [a]	Infrared bands [cm^{-1}] [b]
CH_3	CH_3	120–122	1560
C_2H_5	C_2H_5	51–52	1540
CH_3	C_6H_{11}	97.5–99	1540
C_6H_{11}	C_6H_{11}	131–132	1500 (sh)
CH_3	C_6H_5	ca. 65 (decomp.)	
$R^1 + R^2 = (CH_2)_5$		184.5 (decomp.)	1520
$R^1 + R^2 = (CH_2)_2O(CH_2)_2$		170–172 (decomp.)	1535

[a] Determined in a sealed tube, uncorrected.
[b] Measured in Nujol.

The crystals are mostly colorless and were prepared in quantitative yield in a glove box with absolute exclusion of moisture; they were washed with ether and then freed from adhering solvent in a vacuum desiccator. The BF_3-nitrosamine complexes are strongly hygroscopic.

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German version: Angew. Chem. 75, 1104 (1963)

[1] Short original communication; no extended report will be published.

[2] *S. Hünig, L. Geldern,* and *E. Lucke,* Angew. Chem. 75, 476 (1963); Angew. Chem. internat. Edit. 2, 327 (1963).

[3] *W. S. Layne, H. H. Jaffe,* and *H. Zimmer,* J. Amer. chem. Soc. 85, 435 (1963).

[4] *R. D. Brown* and *G. E. Coates,* J. chem. Soc. (London) *1962,* 4723.

Preparation of True Sodium Hexametaphosphate $Na_6[P_6O_{18}]$

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Of the condensed phosphates with cyclic anions, only the srimeta- and tetrametaphosphates were hitherto known and ttudied. However, in 1956, *Van Wazer* and *Karl-Kroupa* [1] found indications by means of two-dimensional paper chromatography [2] that phosphates with cyclic anions, *i.e.* metaphosphates, with more than four PO_3 groups per anion, are present in solutions and hydrolysates of Graham's salt. This was confirmed in 1961 by *Rudy* and *Ruf* [3].

From new studies of Graham's salt, we have now found that a good paper-chromatographic separation of the metaphosphates up to the octametaphosphate is possible by varying the composition of the eluant. In addition, by rapid heating of anhydrous sodium trimetaphosphate, we succeeded in preparing a Graham's glass in which higher metaphosphates with cyclic anions are considerably concentrated.

Furthermore, by combined fractionating precipitation of aqueous solutions of such preparations with acetone, silver nitrate, and hexamminecobalt(III) chloride, we succeeded in isolating the hexameta- and the pentametaphosphates as such, and the hexametaphosphate in the form of its crystalline hexamminecobalt(III), barium, and silver salts and in preparing pure $Na_6[P_6O_{18}]$ and its hydrate $Na_6[P_6O_{18}]\cdot 6H_2O$. The Debye diagrams of these salts are characteristically different from those of all other phosphates.

Proof of the cyclic structure of the hexametaphosphate is afforded by titration of the free acid with 0.1 N sodium hydroxide; the titration curve shows only strongly acidic P–OH groups.

Weakly acidic P–OH terminal groups, such as those encountered in the chain phosphates, were not found. A dilute aqueous solution of the free acid may be prepared by treating sodium hexametaphosphate with the H-form of Wofatit KPS ion-exchange resin.

Unequivocal proof for the constitution is furnished, just as with trimetaphosphate [4] and tetrametaphosphate [5], by alkaline ring cleavage. In this reaction, the hexametaphosphate is converted into hexaphosphate which, however, undergoes degradation to a small extent by secondary hydrolysis to lower polyphosphates.

The name 'sodium hexametaphosphate' has persisted in the chemical literature since 1849 [6] to denote Graham's salt. This name has now not only lost its significance but is incorrect, misleading, and hence to be avoided.

Received, October 14th, 1963 [Z 601/429 IE]
German version: Angew. Chem. 75, 1175 (1963)

[1] *J. R. Van Wazer* and *E. Karl-Kroupa,* J. Amer. chem. Soc. 78, 1772 (1956); *J. F. McCullough, J. R. Van Wazer,* and *E. G. Griffith* ibid. 78, 4528 (1956).

[2] *J. P. Ebel,* Bull. Soc. Chim. France 20, 991 (1953).

[3] *H. Rudy* and *F. Ruf,* personal communication.

[4] *E. Thilo* and *R. Rätz,* Z. anorg. allg. Chem. 258, 33 (1949).

[5] *E. Thilo* and *R. Rätz,* Z. anorg. allg. Chem. 260, 255 (1949).

[6] *Th. Fleitmann,* Poggendorffs Ann. physik Chem. 78, 233 (1849).

Synthesis of 5-Hydroxymethyl-2′-deoxycytidine

By Dr. R. Brossmer and E. Röhm

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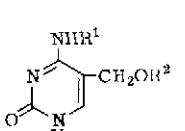
5-Hydroxymethyl-2′-deoxycytidine *(9)* replaces all of the deoxycytidine in the DNA of various bacteriophages and is therefore of special interest.

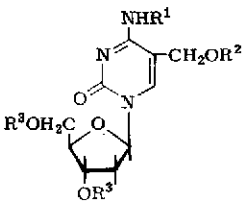
Benzylation of 5-hydroxymethylcytosine gave the benzyl ether *(1)*, m.p. 250 °C (decomp.) in 90 % yield; on subsequent acylation, *e.g.* with benzoyl chloride in pyridine, this afforded *(2)*, m.p. 174–175 °C; in 80 % yield.



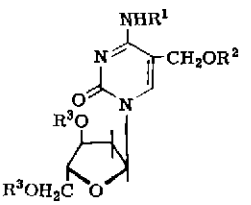
(1) $R^1 = H$, $R^2 =$ Benzyl
(2) $R^1 =$ Benzoyl, $R^2 =$ Benzyl
(2a) $R^1 = R^2 =$ Benzoyl

Compound *(2)* forms a mercury salt *(3)* which is soluble in toluene; condensation of *(3)* with 3,5-di-*p*-toluyl-2-deoxy-D-ribofuranosyl chloride at room temperature affords a mixture of the anomeric nucleosides in almost quantitative yield. Their separation is based on differences in their solubilities: β-anomer *(4)*, m.p. 170–171 °C, $[\alpha]_D^{20} = -52°$ in chloroform; 48 %; α-anomer *(5)*, m.p. 128–129 °C, $[\alpha]_D^{20} = -114°$ in chloroform, 35 %.

In boiling methanol, *(4)* yields 80–85 % *(6)*, m.p. 163–164 °C, $[\alpha]_D^{20} = -42.7°$ in chloroform. Catalytic hydrogenation of *(4)* yields *(7)*, m.p. 151–152 °C, $[\alpha]_D^{20} = -64.5°$ in chloroform, in 86 % yield, and both *(4)* and *(6)* afford, after the removal

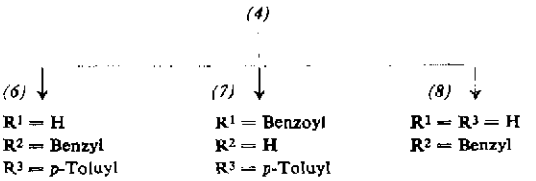


(4) R^1 = Benzoyl, R^2 = Benzyl, R^3 = p-Toluyl



(5) R^1 = Benzoyl, R^3 = Benzyl, R^3 = p-Toluyl

of the acyl residues with sodium methoxide solution, 91 % *(8)*, m.p. 198–199 °C, $[\alpha]_D^{20} = +33°$ in dimethylformamide. Catalytic hydrogenation of *(8)* or treatment of *(7)* with sodium methoxide yields the same free *(9)*, m.p. 203 °C (decomp.), $[\alpha]_D^{20} = +51°$ in water; yield: 35 % based on *(3)*. R_F of *(9)*: 0.16–0.18 in n-butanol/water (saturated), 0.31 to 0.33 in n-propanol/water (5:1) ascending. Ultraviolet absorption of *(9)* at pH 1: $\lambda_{max} = 283$ mμ; 212 mμ; $\varepsilon_{max} = 12.6 \times 10^3$, 11.9×10^3; $\lambda_{min} = 243$ mμ; $\varepsilon_{min} = 1.6 \times 10^3$; A 250/260 = 0.43; A 280/260 = 2.68.



The structure of *(4)* was proved by degradation to β-thymidine. The configuration assigned was supported by the NMR-spectrum. If merely the preparation of the unsubstituted *(9)* is desired, doubly benzoylated *(2a)*, m.p. 154–155 °C, yield: 80 %, is used as starting material; the condensation of *(2a)* to the protected nucleoside, m.p. 181–182 °C, proceeds equally smoothly. Removal of all the acyl groups yields *(9)* in one stage. We shall report soon on the preparation of other hydroxymethylcytosine nucleosides and of nucleotides.

Received, October 15th, 1963 [Z 602/425 IE]
German version: Angew. Chem. 75, 1105 (1963)

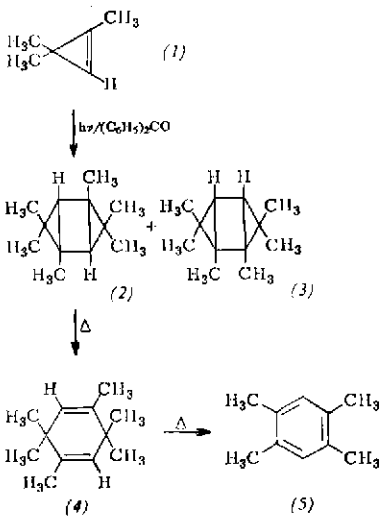
Photochemical and Catalytic Dimerization of 1,3,3-Trimethylcyclopropene

By Dipl.-Chem. H. H. Stechl

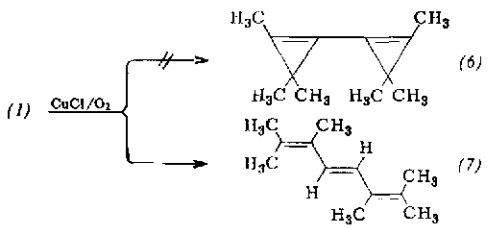
Institut für Organische Chemie der Technischen Hochschule Karlsruhe (Germany)

1,3,3-Trimethylcyclopropene *(1)* [1] dimerizes on irradiation (Hanau high-pressure mercury lamp) in acetone with benzophenone as sensitizer. The dimer (15 % yield after 48 h) consists of a difficultly separable 4:1 mixture of the tricyclic hydrocarbons *(2)* and *(3)* of b.p. 66 °C/17 mm. Unreacted *(1)* can be recovered. Evidence for the structure of *(2)* is derived from its NMR spectrum, which shows singlets at 8.99 τ (bridge protons), 9.12 τ (bridge methyl groups), and at 8.80 τ and 8.89 τ (geminal methyl groups) with area ratios of 2:6:6:6. The signals of *(3)* are at slightly higher field intensities, *viz.* τ = 9.02; 9.12; 8.82; 8.91; its ultraviolet spectrum has $\lambda_{max} = 216$ mμ; ε = 250.

The extinction coefficient is almost twice that of bicyclo-[0,1,2]pentane [2], *viz.* $\lambda_{max} = 216$ mμ; ε = 137. The infrared spectrum shows characteristic bands at 912 cm^{-1} (strong) and 1070 cm^{-1} (weak). Thermal isomerization at 390 °C of *(2)* and *(3)* to durene *(5)* occurs in 40 % yield with the loss of two methyl groups, and probably proceeds via the as yet unknown 1,4-cyclohexadiene derivative *(4)*.



The C–H bond on the ring in *(1)* has 44 % s-character [3]. The expected oxidative coupling which is typical of acetylenes does not occur with *(1)*. Instead, under the catalytic influence of Cu(I) or Cu(II) ions, dimerization occurs and both of the three-membered rings are then opened to give hexamethylhexatriene *(7)*, m.p. 47 °C, yield: 60 % (double-bond bands at 1790 cm^{-1} and 1630 cm^{-1}, strong band at 950 cm^{-1}). The NMR signal of the vinyl protons lies at 3.38 τ. The methyl groups (8.21 τ) appear as broad bands, which cannot be further resolved. The ultraviolet spectrum shows a principal maximum at $\lambda_{max} = 282$ mμ; log ε = 4.75.



The product of Wittig reaction of trimethylacrolein with 1-bromo-2,3-dimethyl-2-butene is identical with *(7)*.

Received, October 17th, 1963 [Z 603/432 IE]
German version: Angew. Chem. 75, 1176 (1963)

[1] *G. L. Closs* and *L. E. Closs*, J. Amer. chem. Soc. *83*, 2015 (1961), and personal communication.

[2] *R. Criegee* and *A. Rimmelin*, Chem. Ber. *90*, 414 (1957).

[3] *G. L. Closs*, Proc. chem. Soc. (London) *1962*, 152.

The Action of Sodium Hydrazide on Amides

By Doz. Dr. Th. Kauffmann and Dipl.-Ing. J. Sobel

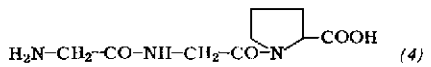
Institut für Organische Chemie der Technischen Hochschule Darmstadt (Germany)

Experiments with *N*-caproylpiperidine, *N*-benzoylpiperidine [1], *N*-benzyl-2-pyrrolidone, glycyl-L-proline, and glycyl-L-4-hydroxyproline have shown that *N,N*-dialkylamides [group $-CO-N(Alk)_2$ *(1)*] are split almost quantitatively by

treatment for 1 hour at 0 °C with sodium hydrazide in ether containing some hydrazine, and subsequent hydrolysis with water [2]:

$$(1) \rightarrow -CO-NH-NH_2 + HN(Alk)_2$$

Amides, such as 2-pyrrolidone, diglycylglycin, capronamide, or asparagine, that contain the groups $-CO-NH-Alk$ *(2)* and $-CO-NH_2$ *(3)* which are able to form mesomeric anions, are stable under these conditions. It was thus deduced that amides containing group *(1)* as well as group *(2)* or *(3)*



(4)

should be split selectively at groups *(1)*; this expectation was fulfilled for the combination *(1)* + *(2)*: On treating diglycyl-L-proline *(4)* for 45 min with sodium hydrazide in ether containing hydrazine, it was converted almost completely into diglycylhydrazine and proline [3]; only traces of monoglycylhydrazine were formed.

It seems promising to attempt to split proteins at the amino acids proline and hydroxyproline with this reagent, because anhydrous hydrazine [4] constitutes an equally good solvent for sodium hydrazide and proteins, and because the natural amino acids, with the exception of those containing sulfur, are stable towards sodium hydrazide at 0 °C.

Received, October 24th, 1963 [Z 605/433 IE]
German version: Angew. Chem. *75*, 1177 (1963)

[1] In addition to benzoylhydrazine, some *N,N'*-dibenzoylhydrazine is formed.

[2] Attempts to induce cleavage with sodamide at 0 °C or 35 °C were unsuccessful.

[3] It is not yet known whether racemization of the L-proline occurs.

[4] Anhydrous hydrazine splits peptide linkages only very slowly at 0 °C.

CONFERENCE REPORTS

Meeting of the Schweizerische Chemische Gesellschaft

August 31st, 1963 in Sitten (Switzerland)

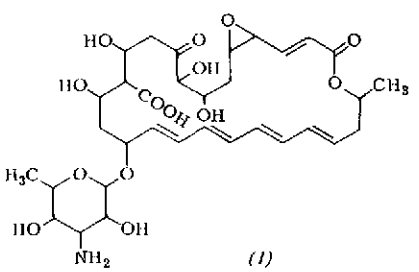
From the proceedings:

The Structure of Pimaricin

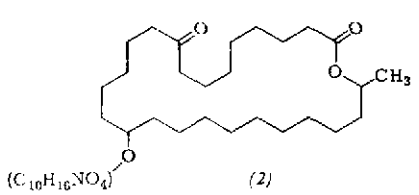
O. Ceder, Stockholm (Sweden)

A reinvestigation of the structure of the polyene antibiotic pimaricin was reported. The results led to the formula *(1)*. The structure is in accordance with a biogenesis from acetate and differs significantly from an earlier proposal [1].

The carbon skeleton and the positions of two carboxyl groups and two oxygen functions in pimaricin were determined by degradation to 12-methylhexacosane, 2-tetradecylundecanedicarboxylic acid, 9-oxohexacosanoic acid, 5,9-epoxyhexacosanoic acid, and hexacosanoic acid. Identification of the compounds mentioned was considerably facilitated by high temperature gas chromatography, as well as NMR and mass spectroscopy. The position of the aminohexose mycos-



(1)



(2)

[1] *J. B. Patrick* and *R. P. Williams*, J. Amer. chem. Soc. *80*, 6689 (1958).

amine and the size of the macrocyclic lactone ring were ascertained by comparison with *(2)*. The positions of the tetraene system and of the remaining oxygen functions were established by chromic acid and periodate oxidations, retroaldol reactions, and spectroscopic methods.

Photoreactions of Nitrogenous Heterocycles

P. Cerutti and *H. Göth*, Zürich (Switzerland)

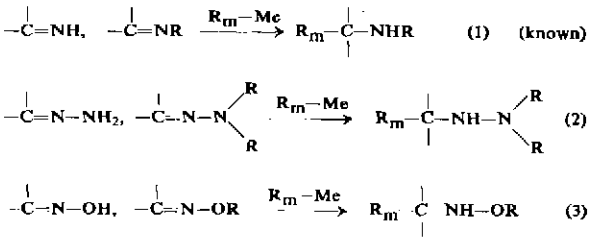
The photoreaction of benzylidene imine derivatives in methanol led to imidazolidine derivatives. Starting from 1-methyl-3,4-dihydroisoquinoline *(1)*, *meso*- and rac-*N,N'*-methylenebis-[1-methyl-1,2,3,4-tetrahydro-1-isoquinolyl] were formed, and 6,7-dimethoxy-3,4-dihydroisoquinoline *(2)* gave *meso*- and rac-*N,N'*-methylenebis-[6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolyl], while *N*-methyliminotoluene gave *meso*- and rac-1,3-dimethyl-4,5-diphenylimidazolidine. The products formed by photolysis of *(1)* and *(2)* were also synthetized by non-photochemical pathways.

The photochemistry of acridine and its derivatives in methanol and ethanol was also discussed. In addition to acridan (9,10-dihydroacridine) and its derivatives, dimeric products coupled in the 9,9'-position were also obtained (*e.g.* 9,10,9',10'-tetrahydro-9,9'-biacridyl from acridine) and identified, particularly by NMR spectra. A topic of special interest is the newly discovered reductive 9-α-hydroxyalkylation of acridine and its derivatives. Starting from the appropriate materials, irradiation in methanol or ethanol led to 9-hydroxymethylacridan, 9-(α-hydroxyethyl)acridan, 9-methyl-9-hydroxymethylacridan, 10-methyl-9-hydroxymethylacridan, 10-methyl-9-(α-hydroxyethyl)acridan, and 9,10-dimethyl-9-hydroxymethylacridan.

Additions onto C=N Double Bonds

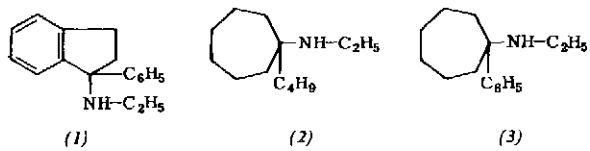
A. Marxer and *M. Horvath*, Basel and Bern (Switzerland)

The object of this research was to add organometallic compounds onto the C=N double bonds of Schiff's bases, hydrazones, and oximes.



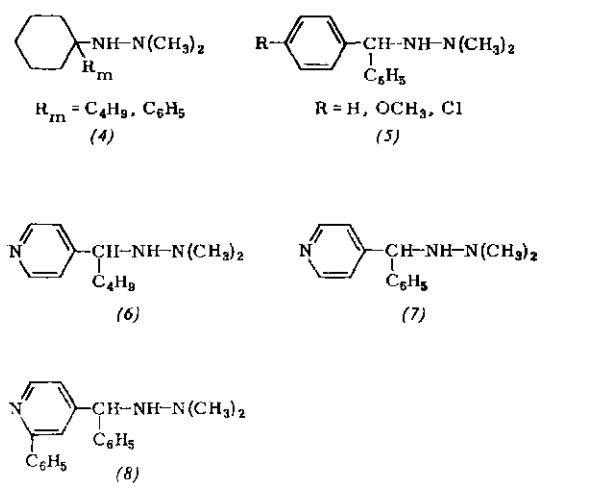
The addition products of hydrazones and oximes were in ract obtained when *N*- and *O*-alkylated starting materials were used.

The Schiff's bases served as test substances and reacted more readily than the hydrazones. Of the organometallic compounds examined, the best yields were obtained from the organolithium compounds. The addition of phenyl-lithium onto iminocyclohexane has already been described by *Godefroi* et al. (Parke Davis). No reaction product could be obtained from iminocyclopentane, although *(1)* was formed from *N*-ethyliminoindane. *N*-Ethyliminocycloheptane yielded *(2)* and *(3)*.



(1) *(2)* *(3)*

Starting from *N,N*-dimethylhydrazonocyclohexane, *(4)* was obtained; benzaldehyde dimethylhydrazone gave *(5)*, and pyridine-4-carboxaldehyde dimethylhydrazone gave *(6)* and *(7)* with *(8)* as a by-product.



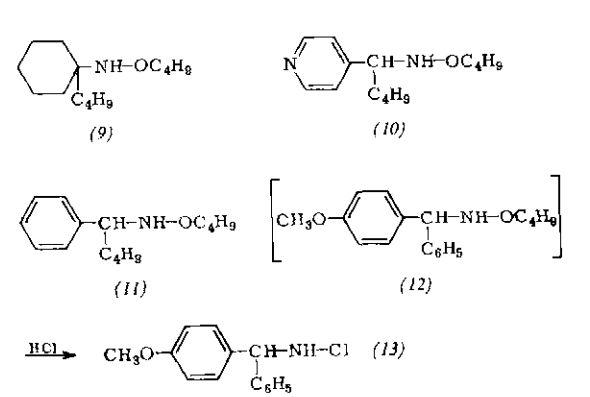
$R_m = C_4H_9$, C_6H_5 *(4)*

R = H, OCH_3, Cl *(5)*

(6) *(7)*

(8)

o-Butyloximes give addition products [*(9)*–*(11)*] with butyllithium only with difficulty, although a vigorous reaction occurs with phenyl-lithium. The *N*-chloroamines later isolated, *e.g.* *(13)*, establish the structure of *(12)*.



(9) *(10)*

(11) *(12)*

(13)

W. Feitknecht and *A. Durtschi*, Bern (Switzerland)

When α- or γ-Fe_2O_3 or the mixed phase γ-Fe_2O_3/Fe_3O_4 (= $Fe_{3-x}O_4$) is heated in a stream of hydrogen at 300–500 °C, Fe_3O_4 is formed first and is then reduced directly to iron. The rate of formation of crystallization nuclei of iron is slow. When finely crystalline oxide is used, the iron nuclei grow even at 300 °C at the expense of numerous microcrystals of oxide as a result of the great mobility of the iron atoms. The iron crystals become considerably larger than those of the oxide and are linked together to form secondary particles of irregular shape. The resultant pyrophoric property is due to the size of the specific surface area of the iron powder. Spontaneous ignition takes place when the surface area is greater than about 3 m^2/g. When pyrophoric iron is inactivated by passing a mixture of nitrogen with a little oxygen over it, its temperature rises steadily to a constant value. The thickness of the oxide layer calculated from the duration of the heating agrees with the analytically determined value of 13 Å. An estimate of the heat generated during the formation of the oxide layer and of the temperature rise caused by it is in agreement with the flash point of inactivated iron powder with a specific surface area of ca. 3 m^2/g.

Redox Reactions in Sapphire

Rudolf Müller, Zürich (Switzerland)

The nickel and cobalt ions present in sapphire can be reduced with hydrogen above 800 °C and 1100 °C, respectively. Yellow, nickel-containing sapphires then become colorless, and green cobalt-containing sapphires become grey-green. On heating in the presence of oxygen, the ions are reoxidized. The process is reversible.

The infrared spectrum of sapphire contains a broad peak at 3000 cm^{-1} with a band-width of 200 cm^{-1}. This band is due to a hydrogen bridge in the sapphire. Besides this $^-O-H\cdots O^{2-}$ stretching frequency, there are also four weaker bands between 2500 and 1900 cm^{-1}. The positions of these bands differ for the Ni- and Co-containing reduced sapphires. This indicates that the hydrogen ions are in the immediate vicinity of the reduced metal ions.

The Ni reduced with hydrogen can be reoxidized by irradiation with a ^{60}Co source. The bands in the infrared between 2500 and 1900 cm^{-1} then disappear, although the hydrogen-bridge bands still remain. The electrons freed by the oxidation of the Ni do not reduce hydrogen ions, but are captured by defects in the crystal.

Macromolecular Organization and the Active Centre of Yeast Hexokinase

A. Ramel, E. A. Barnard, and *H. K. Schachman*, Basel (Switzerland), London (England), and Berkeley (U.S.A.)

Highly active, repeatedly recrystallized hexokinase from baker's yeast can be separated in the ultracentrifuge at pH 7 into two components with sedimentation coefficients of 5.6 S and 3.7 S. In the region of the isoelectric point (pH ≈ 5), the whole material sediments with 5.6 S, and at pH 8 in the presence of glucose with 3.7 S. Sugars which are not phosphorylated by hexokinase have no influence on this transformation. Chromatography, electrophoresis, and end-group analysis have shown that the components are independent of each other and only apparently constitute a monomer-dimer relationship. The same starting material can also be resolved by chromatography into two components (hexokinase A and

hexokinase B), whose behavior in the ultracentrifuge explains the observations on the mixture.

pH 5—8	Glucose	pH 8
Hexokinase A	⟵ ⟶	Hexokinase A'
Mw ≈ 93000		Mw ≈ 50000
dimer, 5.6 S		monomer, 3.7 S
pH 8(7)	$+ H^+$	pH 5
Hexokinase B	⟵ ⟶	Hexokinase B'
Mw ≈ 47000		Mw ≈ 94000
monomer, 3.7 S		dimer 5.6 S

Hexokinase A and hexokinase B dissociate in the presence of Na dodecyl sulfate to give enzymatically inactive subunits, with weight-average molecular weight $M_w \approx 23500$. Hexokinase A thus consists of four and hexokinase B of two polypeptide chains. End-group analysis confirmed this picture of the macromolecular organization of the two isozymes. Titration of the mercapto groups and the kinetics of inactivation show that 1–4 SH-groups per molecule (Mw = 47000) must be involved in the active center or centers, and that these groups become accessible to the usual –SH reagents only above about 30 °C – probably after partial unfolding of the molecule.

The Theory of the Solvent Isotope Effect on Acid-Base Equilibria and on the Rates of Acid-Catalysed Reactions with Pre-equilibria

A. V. Willi, Bern (Switzerland)

From the known difference in the free energies of light and heavy water, a partition function ratio for the liquid phase at 25 °C may be calculated: $Q_{D_2O}/Q_{H_2O} = 1416$. Assuming the constant L = 11.0 for the equilibrium:

$$2\,D_3O^+ + 3\,H_2O \rightleftarrows 2\,H_3O^+ + 3\,D_2O$$

one obtains:

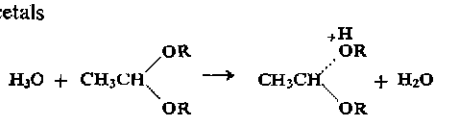
$$Q_{D_3O^+}/Q_{H_3O^+} = 16100.$$

The corresponding partition function ratio for the organic acid ROH follows from the approximation: $Q_{ROD}/Q_{ROH} \approx (Q_{D_2O}/Q_{H_2O})^{1/2}$ in accordance with the assumption that the difference in zero-point energy per OH-bond in ROH is as great as that in H_2O. In the case of cationic acids SH^+ (*e.g.* R_2OH^+ or R_2COH^+, *i.e.* protonated ethers or ketones), the OH-bonding resembles that of the H_3O^+ ion. For these one can write:

$$Q_{SD^+}/Q_{SH^+} \approx (Q_{D_3O^+}/Q_{H_3O^+})^{1/3}$$

From these partition function ratios, the solvent isotope effect on the acidity is $K_H/K_D = 3.3$ for organic acids ROH and $K_H/K_D = 2.2$ for organic cationic acids R_2OH^+ and R_2COH^+, which is in good agreement with experimental data.

In the formation of the transition state of the acid-catalysed hydrolysis of acetals

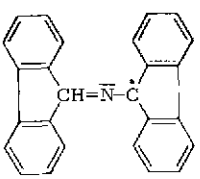


two OH-bonds are completely and another partly converted from a hydroxonium-like into a water-like condition. It follows that the kinetic solvent isotope effect k_H/k_D must lie between 1/3.3 and 1/2.2 (experimental value: 1/2.7). Similar considerations may be applied to the acid-catalysed enolization of acetone, *etc.* [VB 751/105 IE]

German version: Angew. Chem. *76* (1964), in the press.

SELECTED ABSTRACTS

The 2-aza-bis-(2,2'-biphenylene)allyl radical *(1)* prepared by *R. Kuhn* and *F. A. Neugebauer* is identical with the so-called "difluorenyl nitrogen". 2-Aza-1,1,3,3-bis-(2,2'-biphenylene)-propane was converted into the *N*-chloro compound with t-butyl hypochlorite; subsequent treatment of the latter with sodium hydroxide and potassium ferricyanide solution yielded the dimer (overall yield 78 %), which dissociates slightly in

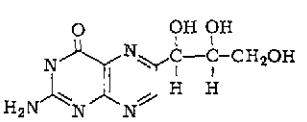


(1)

solution. Hydrogenation over palladium gave fluorene and ammonia. It follows from a discussion of ultraviolet and infrared spectra that *(1)* is a C-radical. / Mh. Chem. *94*, 16 (1963) / –Re. [Rd 614/185 IE]

The geological age of a totally-enclosed salt lake on the Anatolian plateau was determined by *E. Bagge* and *H. Willkomm* on the basis of its ^{36}Cl concentration. ^{36}Cl is a β-emitter with a half-life of 3×10^5 years and is produced from natural Cl by capture of a neutron from cosmic rays. ^{36}Cl is also formed as a result of collisions of argon nuclei with the nucleonic component of cosmic rays and is brought to the ground by rain. The saturation activity of the ^{36}Cl in the salt-lake amounted to $14.1 \times 10^{-3} \pm 1.2 \times 10^{-3}$ disintegrations per g. per min. It was assumed that the rate of production of ^{36}Cl and the water content of the lake was constant during the time of its formation, and that the increase in NaCl content was linear. Before measurement of the activity, the salt was freed from potassium by removal of HCl by treatment with H_2SO_4, followed by combination with NaOH. The specific activity was measured using two photo-multipliers and a liquid scintillator. The probable age of the lake was determined as 0.9×10^6 to 1.4×10^6 and its minimum age as 0.5×10^6 to 0.6×10^6 years. / Naturwissenschaften *50*, 299 (1963) / –Kr. [Rd 604/171 IE]

The constitution and synthesis of neopterine is communicated by *H. Rembold* and *L. Buschmann*. Neopterine *(1)* is a blue fluorescent pterine, found in bee pupae, in royal jelly, and also in traces in worker bees and is 2-amino-4-hydroxy-6-(1,2,3-trihydroxypropyl)pterine. This formula is deduced on the basis of its degradation by permanganate to 2-amino-4-hydroxypteridine-6-carboxylic acid as well as from the ultraviolet spectrum of the compound and its behavior on paper chromatograms. The four isomers arising from the two centers of asymmetry in the molecule (D- and L-*erythro* and D- and L-*threo* compounds) were synthetized by condensing 2,4,5-triamino-6-hydroxypyrimidine with the corresponding

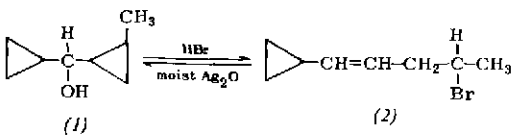


(1)

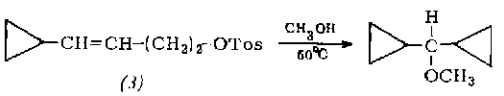
sugars (ribose, xylose, and arabinose). On the basis of its behavior on paper chromatograms in the system isopropanol/aqueous boric acid and of its inactivity in the growth test with the protozoon *Crithidia fasciculata*, compound *(1)* has the D-*erythro* configuration. Compound *(1)* is presumably the first stable product in the purine-pterine conversion and represents a preliminary step in the biosynthesis of biopterine. / Chem. Ber. *96*, 1406 (1963) / –Ma. [Rd 618/186 IE]

A new polysulfuric ester with heparin-like activity has been reported by *R. Pulver, C. Montigel,* and *B. Herrmann.* The heparinoid (G 31150 of J. R. Geigy AG) is prepared from highly esterified pectin of high molecular weight, which is first degraded oxidatively to units of 6–9 galacturonic acids each. After esterification with sulfuric acid, the fragments have average molecular weights of 2500 ± 500 and have only weak anticoagulatory activity. The end groups presumably have the configuration of mucic acid with a carboxylic group, and are hence capable of forming complexes with calcium. Interlinking of the fragments by means of calcium bridges yields a product consisting of chain-like molecules with average molecular weights of 24000 ± 1000. This product shows strong antithrombin activity and counteracts thrombin formation. On local application it has an anti-inflammatory effect. / Arzneimittel-Forsch. *13*, 194 (1963) / –R. [Rd 622/187 IE]

The acid-catalysed ring-opening of 2-methyldicyclopropylmethanol *(1)* has been investigated by *M. Hanack* and *H. Eggensperger.* Following a homoallyl rearrangement with 48 % HBr at 0 °C for 1 hr, *(1)* gives 90 % 4-bromo-1-cyclopropyl-1-pentene *(2)*, which reforms the cyclopropane ring with moist Ag_2O. Thus, ring opening occurs preferentially in the substituted ring, in accordance with Markownikoff's rule.



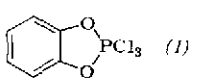
(1) *(2)*



(3) *(4)*

A further example of the preponderant formation of dicyclopropylmethoxyl derivatives from homoallyl compounds is afforded by the methanolysis of 1-cyclopropyl-1-buten-4-yl *p*-toluenesulfonate *(3)* to give dicyclopropylmethyl methyl ether (93 %). In contrast, methanolysis of 1-methyl-1-buten-4-yl and 1,1-dimethyl-1-buten-4-yl *p*-toluenesulfonates yields only 40 % of the cyclopropylmethyl methyl ether alongside 60 % homoallyl methyl ether. / Chem. Ber. *96*, 1259 (1963) / –Ma. [Rd 621/179 IE]

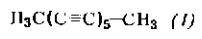
The preparation and preparative use of catechylphosphorus trichloride *(1)* is described by *H. Grosse* and *J. Gloede.* Treatment of pyrocatechol with PCl_3 gives 94 % catechylphosphorus monochloride, which is then dissolved in CCl_4 and treated with Cl_2 with ice-cooling to give 94 % *(1)*, b.p. 132 to 135 °C/13 mm, m.p. 61–62 °C. Compound *(1)* acts as halogen carrier on reaction with compounds with oxygen functions. Carbonyl compounds are converted into geminal dichlorides, or into chloro-olefins by elimination of HCl.



(1)

Acetylated sugars give acetylchloro sugars, carboxylic acids are converted into acid chlorides, and alkyl formates into dichloromethyl alkyl ethers, but other esters yield the acid chloride and alkyl chloride. Amides are dehydrated to nitriles and alkyl chlorides; urethanes and thiourethanes form isocyanates. The yields are always high. Compound *(1)* has several advantages over PCl_5, *e.g.* no oxidative action, ease of weighing, good solubility in inert solvents such as ether, benzene, and chloroform. The catechylphosphorus oxychloride obtained as a by-product is easily removed by distillation or hydrolysis. The reaction products are free from phosphorus. / Chem. Ber. *96*, 1387 (1963) / –Ma. [Rd 617/176 IE]

The poly-ynes present in Flaveria repanda Lag., a native American member of the genus *Heleniae* L., have been described by *F. Bohlmann* and *K. Kleine.* Whereas few acetylenic compounds have hitherto been found in this genus, this plant contains several compounds of this type, albeit in small quantities. In addition to the already known compounds *(1)–(3)*, compounds *(4)–(8)* are found in the root.



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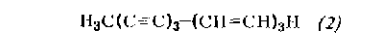

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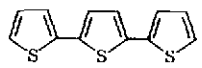

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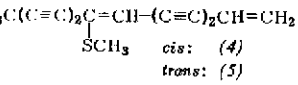
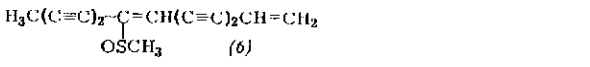
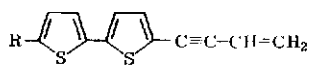


cis: *(4)*
trans: *(5)*



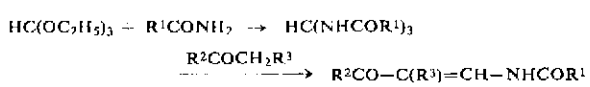
(6)



(7): R = $AcOCH_2$ *(8)*: R = H

The sulfoxide *(6)* is optically active. The biogenetic relationships between compounds *(1)* and *(4)*, *(5)*, and *(6)* are obvious. The occurrence of compound *(7)* is very interesting in this connection, since up till now only compound *(8)* was known, which lacks a methyl group, if one assumes it to be formed from *(1)* by double H_2S-addition. In *(7)* however, this methyl group is present in an oxidized form. Compound *(8)* is probably formed from *(7)* by further oxidation and decarboxylation. Beside chemical reactions, nuclear magnetic resonance spectrosopy played a very important part in the elucidation of the structures of compounds *(4)–(7)*. / Chem. Ber. *96*, 1229 (1963) / –Bn. [Rd 689/189 IE]

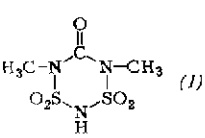
The synthesis and reactions of tris(acylamino)methanes have been investigated by *H. Bredereck, F. Effenberger,* and *H. J. Treiber.* Ethyl orthoformate reacts with carboxylic acid amides in boiling toluene in the presence of acid catalysts to give tris(acylamino)methanes. Aliphatic carboxylic acid amides react smoothly to give yields of 80–90 %. *p*-Nitrobenzamide however reacts poorly, and trichloroacetamide not at all. The higher tris(acylamino)methanes react with aromatic ketones at 150–200 °C in the presence of acids to form β-(acylamino)vinyl phenyl ketones *(1)*, which, if the R^2-substituent has no electron-withdrawing action, in turn afford



(1)

pyrimidines on treatment with formamide, formamidine acetate, or the ammonia produced therefrom on heating. Treatment of *(1)* with guanidine carbonate or hydrazine leads to 2-aminopyrimidines and 2-aminopyrazoles, respectively. / Chem. Ber. *93*, 1505 (1963) / –Ma. [Rd 687/190 IE]

A new six-membered ring system containing sulfur was obtained by *M. Becke-Goehring* and *H.-A. Schlotter* as the dimethyl derivative *(1)*, m.p. 157 °C (decomp.), by reaction of imido-bis-sulfuryl chloride with *N,N'*-dimethylurea. The



(1)

strongly acidic compound forms a trimethyl derivative, m.p. 150.5 °C which crystallizes well. The infrared spectrum is in accordance with the constitution. / Naturwissenschaften *50*, 353 (1963) / –Ma. [Rd 616/175 IE]

Chemische Transportreaktionen, der Transport anorganischer Stoffe über die Gasphase und seine Anwendungen (Chemical Transport Reactions; Transport of Inorganic Materials via the Gas Phase and its Applications), by *Harald Schäfer*. "Angewandte Chemie" and "Chemie-Ingenieur-Technik" Monograph No. 76. Verlag Chemie GmbH, Weinheim-Bergstr. 1962. 1st Edit., 142 pp., stiff covers. DM 16.80 (about $4.25).

"The Transport of Inorganic Substances through the Gas Phase, and Its Applications" is the subtitle of this work which will be of great interest to the thermodynamist, which offers an abundance of material for the inorganic chemist, and which will fill the chemist engaged in the preparation of inorganic compounds with enthusiasm!

Chemical transport reactions depend upon the reaction of a solid (or liquid) substance with a gaseous one leading to the formation of exclusively gaseous products; in the simplest case: $A_{(s)} + nB_{(g)} \rightleftharpoons AB_{n\,(g)}$. If the forward reaction is endothermic, then A migrates along the temperature gradient from higher to lower temperatures. The phenomenon resembles sublimation, but is basically a chemical reaction. If, however, the forward reaction is exothermic, then the equilibrium is displaced to the left on increasing the temperature; substance A removed from the gas phase at low temperatures is then – conversely to the above – separated out as a solid again at higher temperatures.

The possibility of chemical transport was already recognized 100 years ago by *Bunsen* and *Sainte-Claire Deville* as well as by *Troost* and *Hautefeuille*. However, even more recently such observations have been limited to isolated cases. It is to the author's credit that he has recognized the wide range of transport reactions and, with numerous collaborators, has clarified the qualitative and quantitative principles involved and examined numerous examples. It is surprising how many problems of widely varying kinds can be solved rapidly by means of transport reactions, *e.g.* the resolution of a complicated juxtaposition of several equilibria, new ways of ascertaining thermodynamic data, the growth of well-formed crystals often of very high purity, and the preparation of materials which are stable only within a limited region, *etc.* The book deals with such topics in a manner which is both lucid and stimulating. *Werner Fischer* [NB 37/51 IE]

Elektrochemische Kinetik (Electrochemical Kinetics) by *K. J. Vetter*. Springer-Verlag, Berlin-Göttingen-Heidelberg 1961. 1st Edit., XV, 698 pp., 342 illustr., cloth-bound, DM 156.– (about $ 40.–).

The great impetus in fundamental electrochemical research after the second world war was directed predominantly towards electrode kinetics. Interest in this subject has recently been greatly stimulated by the increasing analytical and industrial uses of electrochemistry, and by current efforts to develop technically useful fuel cells. Up to now there has been no comprehensive text book on modern electrochemical kinetics. This book by Prof. *Vetter*, who has himself taken a leading part in developments in this field over the last twenty years, brightly fills this gap.

The book comprises the following sections: 1) Electrochemical thermodynamics, including the theory of diffusion potentials, the electrolytic double layer, and electrocapillarity (99 pp.); 2) the theory of overvoltage (207 pp.), including a detailed discussion of the more important causes of polarization (mass transport, energy of activation of charge transfer, homogeneous preceeding and ensuing reactions, crystallisation, ohmic resistance); 3) methods of determining electrochemical reaction mechanisms (42 pp.), with a detailed discussion of differentiation between the various kinds of overvoltage and the determination of the order of reactions; 4) experimental results: in this, the longest section (232 pp.), metal ion electrodes (with and without surface layers), redox electrodes, the hydrogen electrode (to which about 90 pp. are devoted), the oxygen electrode, *etc.* are dealt with; 5) mixed potentials and electrochemical corrosion (14 pp.); and 6) metal passivity (40 pp.).

The extensive pertinent literature has been considered in detail, and data spread throughout many journals have been gleaned together to produce a substantially homogeneous unit which forms a well-integrated work. It may be thoroughly recommended to anyone with an interest in electrochemical kinetics. The printing and layout are good. The high price is regrettable. *N. Ibl* [NB 67/57 IE]

Fortschritte in der Kinetik der homogenen Gasreaktionen, (Advances in the Kinetics of Homogeneous Gas Reactions) by *Z. G. Szabo*, Vol. 6 of the series "Fortschritte der physikalischen Chemie" (Advances in Physical Chemistry), edited by *W. Jost*. Dr. Dietrich Steinkopff Verlag, Darmstadt, 1961. 1st Edit., XII, 239 pp., 15 illustr., 53 tables, cardboard, DM 40.– (about $ 10.–).

In the present 6th volume of the series "Fortschritte der physikalischen Chemie", the author reviews the latest experimental developments and results in the field of homogeneous gas reaction kinetics. The presentation follows the arrangement of *Schuhmacher*'s well-known book. The current state of this field, which is being studied particularly intensively in the U.S.A., Russia, and Great Britain, is explained in the light of over 1000 papers from the period between 1938 and 1959, the bulk dating from the fifties. On account of the limited space available, oxidation reactions, photochemical and radiochemical processes, and isotope reactions have either not been considered or only marginally.

The first part of the book discusses some general aspects of the study of gas reactions and the assessment of data from actual determinations; these are illustrated by some experimental results. Theoretical considerations of the problems of energy transfer and the speed of chemical reactions could naturally only be indicated briefly in this short description. The second part of the book (150 pages) compactly assembles numerous gas reactions and their mechanisms. Not only does the arrangement of the extensive material according to the type of reaction concerned together with numerous summarical tables allow useful and sometimes quantitative comparisons of similar elementary reactions to be made but, together with the very clear index, it helps the reader to gain a quick appreciation of the material presented.

With this volume, which is the only modern text book on the subject in German, the author has not merely given a good review of the progress in homogeneous gas reaction kinetics, he has also created a truly time-saving work of reference for the experimental scientist. *H. Gg. Wagner* [NB 57/56 IE]

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